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ANNUAL SUMMARY REPORT

25 September 1981

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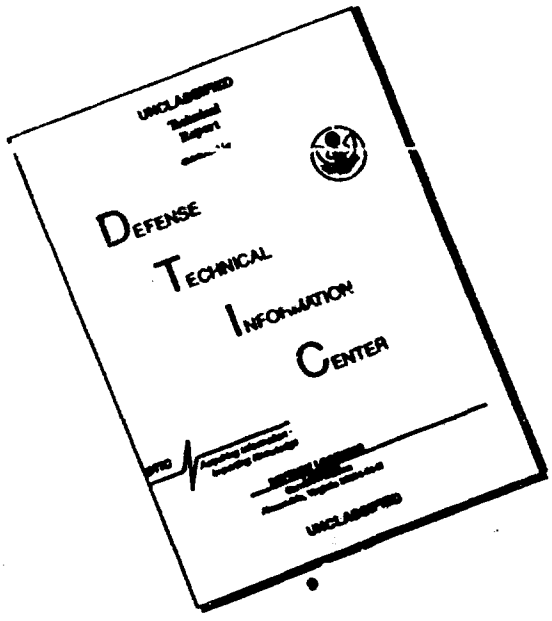

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REPORT NUMBER 1

Anesthesia in a Combat Environment

Annual Summary Report

Richard B. Weiskopf, M.D.

25 September 1981

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contact No. DAMD 17-80-C-0153

University of California
San Francisco, CA 94143

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This research attends to unmet requirements in the physiological management of moderately and severely wounded soldiers, thereby (a) improving the return-to-duty rate of the combat-injured, (b) reducing morbidity and mortality of the combat-injured, and (c) reducing resource (primarily materiel and logistical support) utilzation by Army medical field facilities. The research examines the interaction of anesthetic agents appropriate for

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use in a combat environment, with hemorrhage. In doing so, the physiological processes that contribute to the differences among anesthetic agents for induction and maintenance of anesthesia during hemorrhage will be defined. Swine are used as the experimental model, examining the rationale and physiology of use of nitrous oxide, enflurane, isoflurane, halothane, thiopental and ketamine for induction of anesthesia during the hypovolemic condition.

The products of this project will be important and meaningful data and recommendations to be provided USAMRDC, AHS, and ultimately the user--the anesthetist in a combat environment--regarding use (potential advantages and disadvantages) of anesthetic agents for acutely injured soldiers.

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The products of this project will be important and meaningful data and recommendations to be provided USAMRDC, AHS, and ultimately the user--the anesthetist in a combat environment--regarding use (potential advantages and disadvantages) of anesthetic agents for acutely injured soldiers.

4. FOREWORD

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

5. Table of Contents

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7. Body of Report

A. Background:

1. Overall Objectives:

The long-term objectives of this research project are to improve the physiological management of moderately and severely injured soldiers, and thereby (a) improve the return-to-duty rate of the combat-injured, and (b) reduce morbidity and mortality of the combat-injured. Certain portions of the project also focus on attempts to reduce resource (primarily materiel and logistical support) utilization required for accomplishment of (a) and (b) above.

This research examines the interaction of anesthetic agents appropriate for use in a combat environment, with hemorrhage. In doing so, we also attempt to define the physiological processes that contribute to the differences among anesthetic agents during hemorrhage and the differences between the physiological effects of anesthetics during normovolemia and during hypovolemia. It is hoped that improved management will result from such an understanding.

2. Introduction:

Further advances for forward resuscitation and in management of the combat-wounded will depend, in part, on the acquisition and application of physiological principles and understanding of the interaction of anesthetic agents and techniques with physiology and pathophysiology.

Within the past twenty years, there has been a vast proliferation of research in anesthesia and anesthesia-related fields. Despite the information gained, the paucity of knowledge upon which anesthesiologists must base crucial, life-determining decisions regarding the anesthetic care of the acutely wounded soldier is distressingly evident in the chapter on "Anesthesia and Analgesia" of the First US Revision of the Emergency War Surgery NATO Handbook (2). The NATO handbook quite accurately reflects, "In the wounded who require surgery, the most significant alterations in physiology involve the circulatory and respiratory systems." The anesthesiologist in a combat environment, in order to be able to make intelligent, informed decisions for the proper care of his patient, must have the knowledge of the appropriate normal physiology, abnormal pathophysiology, and how both are altered by the drugs, agents, and techniques he may utilize.

In addition to ensuring adequate ventilation and gas exchange, the anesthesiologist must also be concerned with optimizing cardiovascular function and selecting agents and techniques that will provide the appropriate alterations in cardiac output, peripheral vascular resistance, total body oxygen consumption, systemic blood pressure, myocardial work, myocardial oxygen consumption, and pulmonary vascular resistance. Lacking the

ability to create appropriate alterations, he should, at the worst, have the ability to select the agents and techniques that will do the least harm. Myocardial, cerebral, and peripheral tissue blood flow must be maintained at levels sufficient for aerobic metabolism.

All anesthetic agents have profound influence on all the variables listed above. Halothane, fluroxene, diethyl ether, and cyclopropane, in normal, healthy, young male human volunteers, all elevate mean right atrial pressure, increase skin blood flow and decrease oxygen consumption and base excess (3-11). Ether, fluroxene, and cyclopropane cause minimal or no decrease in cardiac output, stroke volume, left-ventricular work, stroke work, and mean arterial pressure (5). Halothane, fluroxene, and ether decrease total peripheral resistance, while cyclopropane significantly increases it. Unlike other anesthetic agents, deep fluroxene anesthesia causes a rise in arterial pressure (3-5) as a result of increased central sympathetic outflow (12).

Enflurane during spontaneous ventilation results in increased $PaCO_2$, greatly decreased systemic vascular resistance, reduced mean arterial blood pressure and stroke volume, but an increased heart rate and cardiac output (13). The investigators attributed the latter to be a result of "beta-sympathetic-like-stimulation" in response to elevated arterial CO_2 concentrations. When ventilation is controlled so that PCO_2 is normal, cardiac output decreases in comparison with the awake state.

Isoflurane, a relatively new inhalational agent, which has been released recently by the FDA for noninvestigational use, has been shown in unpremedicated, healthy young male volunteers to preserve cardiac output unchanged, decrease stroke volume, arterial pressure, peripheral resistance, $\dot{V}O_2$ and left-ventricular work, while increasing right atrial pressure and $\dot{Q}/\dot{V}O_2$ during constant $PaCO_2$, maintained by controlled ventilation (14). During spontaneous ventilation, cardiac output and heart rate rise further as a result of rise in $PaCO_2$, despite the blunting of the cardiovascular response to CO_2 by isoflurane (15).

Nitrous oxide, first prepared by Priestly in 1772, and first demonstrated to have anesthetic properties by Sir Humphrey Davey in 1800, is not sufficiently potent for sole use as an anesthetic agent. Hyperbaric studies have demonstrated that at normal barometric pressure approximately 110% N_2O would be required to produce anesthesia. Nevertheless, N_2O is almost universally added to other inhalation agents to reduce the concentration of the other inhalation anesthetic. The rationale for this practice was originally related to the now-discarded belief that N_2O, beyond its analgesic/anesthetic properties, had no other pharmacological actions. Within the past 10-15 years, information has been gathered regarding cardiovascular actions of N_2O in experimental animals as well as in man. Because of the wide variations in experimental designs, the results are not clear. Many variables appear to influence greatly the cardiovascular action of N_2O, e.g., type of ventilation, prior administration of drugs, background anesthetic agent, duration of administration

of N_2O prior to measurement, patient age, and patient physical status. Smith et al. (16) also suggested (without supporting evidence or citation of any references) that the "extent of . . . trauma or blood loss" probably influences the cardiovascular action of N_2O. When added to halothane, N_2O appears to result in cardiovascular stimulation in normal man (17,18), in cardiac patients (19), and in the normal dog (20-22), although Hill et al. (23) noted cardiovascular depression with the addition of N_2O to halothane in patients with heart disease (for operation for aortic or mitral valve replacement or coronary artery bypass graft), and Brower and Merin (24) failed to note significant cardiovascular action of N_2O upon its addition to halothane anesthesia in swine. Stimulation is seen in man with the addition of nitrous oxide to fluroxene (25), diethyl ether (26), and isoflurane (27) anesthesia. In contrast, Smith et al. (16) recently observed minimal cardiovascular changes with the addition of N_2O to enflurane anesthesia. With the addition of N_2O to a background of narcotic anesthesia, cardiovascular depression is frequently noted in man (28,29) and in dogs (30).

Cardiovascular stimulation in man by the addition of N_2O to all inhalation anesthetic agents except enflurane is likely an indirect effect. Nitrous oxide was previously thought to spare the myocardium of depression and cause a minimal peripheral vasoconstriction (31-33), probably through an increase in sympathetic activity (32). Recent work has demonstrated a direct decrease in myocardial contractile force by 50% N_2O (34). This is not as great a reduction as caused by an equipotent anesthetic concentration of halothane (34,35). In in vivo studies, the stimulation of sympathetic nervous activity by N_2O would tend to antagonize the direct myocardial depression (36,37).

Despite the stimulation seen, it appears that N_2O does not enhance the overall margin of safety of inhalation anesthetic agents with respect to the amount of agent required to produce respiratory or cardiac arrest (38). Nevertheless, N_2O continues to be used ubiquitously unless the patient physiologically requires very high concentrations of inspired oxygen.

The stimulatory response requires a system capable of providing a relatively intact sympathetic response. This may be neither true nor desirable during hypovolemia. This consideration does not appear to have been tested.

With the introduction of thiopental, induction of anesthesia by intravenous anesthetics became popular. With the entry of the U.S. into World War II, much debate, based on anecdotal experience, arose regarding the wisdom of the use of thiopental in a military setting (39-50). The predominant opinion appears to have been that thiopental should not be used for induction of anesthesia in cases of severe trauma or shock (43,45). However, anesthetic practice today differs greatly from that employed in the early 1940s. At that time, supplemental oxygen was not administered to all patients; nor was it even available on a routine basis. Patients breathed spontaneously. The doses of thiopental that were employed (minimum of 0.5 grams; most often several grams) are by today's standards, grossly excessive, especially for patients with abnormal hemodynamics.

Although thiopental did become the subject of research centered on its hemodynamic properties indicating myocardial depression (51) and reduction of vasomotor tone (52), its use for induction during hypovolemia has not been studied systematically.

More recently, a relatively new agent, ketamine, has been advocated for use in hypovolemic shock (53). In doses of 2 mg/kg IV, given to fit patients without premedication, ketamine has been shown to increase heart rate 36%, systolic blood pressure 41%, diastolic blood pressure 40%, mean arterial pressure 40%, cardiac output 57%, and stroke volume 22% (54,55). This effect is probably mediated through vagolytic activity through baroreceptor blockade (56-58) and central adrenergic stimulation with peripheral alpha effect (56,59-62). Low doses (1-2 mg/kg IV) result in a variable positive inotropic effect (63,64), whereas high doses are negatively inotropic (65-67). Unfortunately, ketamine is relatively short-acting (20-30 minutes), and repeat injections have been reported to have less or no pressor response (54,68,69). Premedication with atropine attenuates the cardiovascular response to ketamine (70-73). When ketamine is given during general anesthesia, a depressor response is elicited (74-76).

Ketamine has been used as an induction agent for hypovolemic shock. In dogs, Virtue et al. (67) noted a modest (4%) increase in blood pressure, and Gassmer et al. (77) noted an increase in blood pressure and heart rate in hypotensive cats on induction with ketamine. These studies, however, did not quantitate the degree of hypovolemia. In 30 humans in "hemorrhagic shock", Corssen et al. (78) reported a 17% increase in systolic blood pressure upon induction with an unspecified dose of ketamine. Chasapakis et al. (79) noted a similar response in 13 similar patients premedicated with atropine and given ketamine 2 mg/kg IV and pancuronium 4 mg IV for induction. Unfortunately, none of these studies quantitated the degree of hypovolemia nor commented upon continued intraoperative course; nor did they compare ketamine with other agents. Most of this literature regarding ketamine has been of less than good quality.

With the exceptions noted, the pharmacology described above was learned from anesthetizing either normal animals or normal, young, healthy men. It is inappropriate to attempt to translate these pharmacological findings from normal man to hypovolemic man. Many of the indirect but important cardiovascular actions of anesthetic agents, especially those of enflurane, isoflurane, nitrous oxide, and ketamine, require an intact sympathetic response. Hemorrhage results in sympathetic discharge (90). Further sympathetic outflow may be neither possible nor desirable.

Only two studies have compared anesthetic agents during hemorrhage (81,82). Theye et al. (81) compared survival times during removal of 0-40 $ml \cdot kg^{-1}$ of blood from dogs with intact spleens, ventilated and anesthetized with cyclopropane, halothane, or isoflurane. Prior to blood loss, cyclopropane resulted in higher cardiac output and mean arterial blood pressure than either halothane or isoflurane, presumably as a result of higher arterial epinephrine concentration. With hemorrhage, cardiac output

and mean arterial blood pressure fell more rapidly with cyclopropane than with either inhalation agent; arterial epinephrine increased more rapidly with cyclopropane than with either inhalation agent; oxygen consumption fell the most and arterial lactate concentration increased the most with cyclopropane. Survival time was shorter with cyclopropane than with either isoflurane or halothane.

We have compared, in splenectomized dogs, the cardiorespiratory influences of graded hemorrhage (0, 10, 20, and 30% blood loss) during enflurane, halothane, isoflurane, and ketamine anesthesia with spontaneous ventilation (82). Diethyl ether and cyclopropane were not studied because of their flammability and explosive potential and, therefore, impracticality in a battlefield medical facility environment. In comparison with the awake state during normovolemia, of the agents studied, only ketamine provided cardiovascular stimulation (increased heart rate and cardiac output), while enflurane resulted in the greatest depression of cardiovascular function (decreased mean arterial blood pressure, cardiac output, and stroke volume). With graded blood loss, cardiac output decreased more rapidly with ketamine than with all of the three inhalation agents, so that by 30% hemorrhage there was no difference in cardiac output among halothane, isoflurane, and ketamine. In response to hemorrhage, systemic vascular resistance increased most with ketamine. Thus, at 30% blood loss, mean arterial blood pressure was highest with ketamine. Rate-pressure product and minute work were highest with ketamine throughout hemorrhage except for minute work at 30% blood loss. This was reflected in total body oxygen consumption being highest with ketamine at 0-20% blood loss. Oxygen consumption did not change with hemorrhage with any inhalation agent, but decreased with hemorrhage with ketamine, suggesting that oxygen demand was not met; arterial blood lactate concentration increased with hemorrhage only with ketamine. Under these conditions of the experiments of Theye (81) and our own (82), sympathetic stimulation appears to be an undesirable property of an anesthetic agent when used for maintenance of anesthesia during moderate hypovolemia. These experiments (82) were performed while the dogs breathed spontaneously, and resulted in differing arterial PCO_2 among the anesthetic agents. Although the cardiovascular stimulation caused by carbon dioxide (15,82) is blunted by anesthetic agents (15,18,83,84), the varying levels of CO_2 among the agents may have influenced the results.

The renin-angiotensin (R-A) system also plays an important role in the physiologic response to and compensation for hemorrhage (86-91). The influence of anesthetic agents on the R-A system has received some attention, with conflicting results (92-98). However, under normal circumstances, the R-A system appears not to be an important controller of cardiovascular dynamics during anesthesia (97). This is not the case, however, in some specific circumstances of altered cardiovascular dynamics. When hypotension is intentionally created by vasodilation with nitroprusside in anesthetized animals, the R-A system plays an important role in preventing what would otherwise be a far greater fall in systemic blood pressure (i.e., it produces significant compensation) (99-100). The R-A system is also responsible for the rebound hypertension observed following discontinuation of

nitroprusside (101-102). In sodium-depleted animals, the R-A system is an important regulator of blood pressure during anesthesia (103). These lines of evidence, indicating that anesthetic agents decrease blood pressure in states where the R-A system is activated, lead one to suspect that this may also be the case during hemorrhage. Although this hypothesis has also been suggested by others (97), it does not appear to have been tested.

Understanding the interaction of anesthetic agents with the R-A system during hemorrhage offers the possibility of improved casualty management through appropriate selection of anesthetic agents and R-A stimulants or blockers.

There is no scientifically derived information regarding the actions of anesthetic agents when used for induction of anesthesia in a hypovolemic condition. The work described in this report represents the initiation of efforts to delineate the interactions of anesthetic agents and cardiovascular control mechanisms and effects during significant hypovolemia.

B. Approach:

Young domestic swine (Chester-White-Yorkshire mix breed; 18-21 kg) are being used to investigate the cardiovascular and metabolic response to induction of anesthesia during hypovolemia. We use swine because (a) dogs are becoming increasingly difficult to obtain for purposes of research; (b) swine are readily available in nearly uniform size; (c) in cardiovascular physiology, the swine more closely resembles man than does the dog; (d) swine hemorrhage models have been used successfully by others. Although we were not aware of it at the initiation of this project, Hannon at the Letterman Army Institute of Research has had good results bleeding awake swine of approximately the same size we use (104-105). His animals have been bled by as much as 50% of their estimated blood volume while unanesthetized and unrestrained. von Engelhardt reviewed the cardiovascular parameters of swine, although much of the data was accumulated in anesthetized animals (106). Awake swine have been used to investigate renal blood flow at rest and during exercise (107), capillary flow during hemorrhagic shock (108), humoral response to hemorrhage (109), and myocardial metabolism after hemorrhage (110). The anesthetized pig has been used for a variety of studies, including hemorrhage (111-117), efficacy of stromal-free hemoglobin (118), and myocardial effects of anesthetic agents (119).

Our animals are first briefly anesthetized with an inhalation agent to allow for placement of peripheral venous, arterial, and thermistor-tipped pulmonary arterial cannulae. The trachea is intubated, the animal paralyzed and ventilated with a tidal volume of 20 ml/kg, and ventilatory rate adjusted to maintain arterial PCO_2 at 40 torr.

Inspired partial pressure of oxygen in arterial blood (P_IO_2) is adjusted to maintain partial pressure of oxygen in arterial blood (PaO_2) at approximately 150 torr. The balance of inspired gas is nitrogen. End-tidal partial pressures of O_2, CO_2, N_2, N_2O, isoflurane, enflurane, and halothane are monitored at the endotracheal tube orifice by mass spectroscopy. The pig is paralyzed with metocurine, 0.2 mg/kg^{-1} IV, and supplemented as required. Metocurine is used because of its lesser cardiovascular effects when compared with pancuronium, gallamine, or d-tubocurarine (120). A percutaneous venous catheter is placed in a forelimb and a femoral arterial catheter is placed percutaneously. A thermistor-tipped flow-directed Swan-Ganz catheter is introduced percutaneously through a femoral vein into the pulmonary artery. Placement is verified by pressure trace and the ability to obtain pulmonary arterial (capillary) wedge pressure. Throughout these experiments, each dog's temperature (measured by the PA catheter thermistor) is maintained within $\pm$ 1 C° of the animal's original temperature. Following placement of all cannulae and elimination of anesthetic agents by continued ventilation,

measurements are made in the normovolemic condition. Samples are withdrawn from the femoral arterial and pulmonary arterial catheters for measurement of arterial and mixed venous blood gases, pH, and oxygen concentration. Blood gases are measured by Radiometer electrodes in Radiometer steel-and-glass cuvets; pH is measured with a Severinghaus-UC electrode (121), all thermostatically controlled at 37° C. Oxygen concentration is measured by an electrolytic cell (LEX-O_2-Con-TL) (122). As an indicator of tissue oxygenation, blood samples are also withdrawn for the measurement of lactate and pyruvate concentrations. To assess each anesthetic agent's influence on the sympathetic response to hemorrhage, blood is sampled for measurement of total catecholamine, epinephrine, and norepinephrine concentrations (123). To assess experimental effects on the renin-angiotensin system, arterial blood is sampled for assay of plasma renin activity (124). Femoral arterial and pulmonary arterial blood pressures are continuously transduced by Statham 23Db transducers. Pulmonary arterial wedge pressure is measured by inflation of the balloon of the pulmonary arterial catheter. Right atrial pressure is measured via the proximal lumen of the Swan-Ganz cannula. Cardiac output is estimated by a thermodilution technique, injecting 3 ml of 0° C 0.9% saline through the pulmonary arterial catheter, and using an analog computer (Edwards Laboratories Model 9520A). Electrocardiogram is constantly monitored.

The following variables are recorded on a multi-channel polygraph and on an FM magnetic tape recorder for later playback as required, and for playback to a digital computer (N.B.: the digital computer belongs to another laboratory and is not available during experimental periods): partial pressures of oxygen, carbon dioxide, nitrous oxide, enflurane, isoflurane, and halothane at the tracheostomy tube orifice; femoral and pulmonary arterial blood pressures (phasic; mean pressures are electrically generated by the pre-amplifier; pulmonary arterial wedge pressure and right atrial pressure are recorded on the same channel as phasic and mean pulmonary artery pressure); electrocardiogram; thermodilution trace from the PA catheter thermistor--necessary to ensure that the washout is logarithmic and that the computer-derived cardiac output value is valid. From these measurements, the following are calculated: base-excess (125-126), stroke volume, mean arterial and pulmonary pressure, stroke and minute myocardial work, systemic and pulmonary vascular resistances, total-body oxygen consumption (cardiac output x $Ca\text{-}\bar{v}O_2$) oxygen transport, and ratio of oxygen transport to oxygen consumption. Following these measurements, the pig is bled during a 30-minute period of 30% of its blood volume (106) through the arterial catheter into a transfer pack containing heparin so that the final concentration of heparin is 1 unit heparin/ml of blood. After a minimum of 30 minutes, all measurements are repeated. Thus, we evaluate each swine awake in the normovolemic condition, and following 30% hemorrhage.

Each pig is randomly assigned to one of the anesthetic groups (each having 10 swine) listed below. With the animal hypovolemic, we then induce anesthesia with one of the following:

Group I: Control; no anesthetic agent administered

Group II: Enflurane, 1.25 % end-tidal

Group III: Halothane, 0.50% end-tidal

Group IV: Isoflurane, 0.85% end-tidal

Group V: Nitrous oxide, 60% end-tidal

Group VI: Ketamine (for IV dose, see below)

Group VII: Thiopental (for IV dose, see below)

The concentrations of inhalation agents have been selected to be slightly greater than one-half the required minimal alveolar concentration in the normovolemic animal [hypotension reduces anesthetic requirement (127)]. The doses of injectable agents (thiopental and ketamine) are established in the following manner. Twenty-four to 48 hours before experimentation, with the pig (normovolemic) resting quietly in a sling, the amount of intravenous agent required to produce loss of lid and corneal reflexes and loss of response to ear-pinch is determined. The dose used for induction of anesthesia during hypovolemia is one-half the dose established during normovolemia 24-48 hours previously. Ear-pinch following induction with this dose during hypovolemia has failed to elicit any response.

End-tidal gas partial pressures, systemic and pulmonary artery pressures, and ECG are continuously recorded during induction. $\dot{Q}$, PAPw, and RAP are measured every 5 minutes during induction of anesthesia.

All measurements, calculations, and blood samplings (as indicated above for the awake conditions) are performed at 5 and 30 minutes after induction of anesthesia. In this way, both the transient and quasi steady-state conditions are assessed.

Following these measurements, shed blood is returned, and after 30 minutes, all measurements, samplings, and calculations are repeated. Anesthesia is then discontinued and calculations repeated 15 minutes after the elimination of the anesthetic agent.

This experimental approach will allow us to show the influence of time (physiologic compensation, or deterioration, if any) on the preparation by comparison of data obtained during the course of experimentation within the control group, and by comparison, within each anesthetic group, of the awake normovolemic values prior to hemorrhage with similar values after return of shed blood and elimination of anesthetic agents.

The data will show the comparative cardiovascular influence of anesthetic agents used for induction of anesthesia during significant hypovolemia.

These results will allow us to provide recommendations to USAMRDC regarding choice of anesthetic agents for use for induction of anesthesia in a wounded soldier who is hypovolemic, and whose blood volume cannot be adequately restored prior to surgery. These results may also allow us to assess the efficacy of N_2O during hypovolemia and to make a recommendation regarding the continuation of supplying N_2O to a battlefield medical facility.

Statistical Treatment of Data: Cardiovascular and metabolic variables among anesthetic agents and the control group will be compared using analysis of variance with repeated measures, and Neuman-Keuls method of multiple comparisons (128). Similar statistical tests will be performed to compare the awake hypovolemic with the anesthetized hypovolemic state, as well as the awake normovolemic with the awake hypovolemic state. These tests will be conducted as the series of experiments progresses, and the experiments will be terminated upon achieving statistical significance ($P < 0.05$) among anesthetic agents, thus affording the possibility of using fewer than the stated number of animals.

C. Results:

1. Awake Hemorrhage:

We have successfully established the awake hemorrhagic swine model in our laboratory. Loss of 30% of estimated blood volume results in physiologic sequelae similar to those occurring in other laboratory animals and man. Data are shown in table 1 (p 31). Thirty per cent hemorrhage causes decreased right- and left-sided filling pressures (right atrial and pulmonary arterial wedge pressures), resulting in a 44% decrease in cardiac output. Despite an increase in plasma renin activity and catecholamine concentration, resulting in increased systemic and pulmonary vascular resistances, compensation was inadequate. Mean arterial blood pressure fell 27%, and mean pulmonary arterial pressure, 28%. Although total-body oxygen consumption did not change, systemic hypoperfusion was evident from increased blood lactate concentration and decreased base excess.

2. Induction of Anesthesia during Hypovolemia:

We have now completed approximately two induction experiments with each agent. Although it is too early to apply statistical analysis to the results, some general trends appear. The control animals (no anesthetic administered) show stable results with time. All agents (including ketamine) appear to result in hypotension following induction during hypovolemia. The mechanisms causing hypotension may not be the same for all anesthetics.

D. Discussion:

The swine appears to be a quite satisfactory animal for laboratory investigations involving hemorrhage. Swine are more readily available than dogs, and in more uniform size. Their cardiovascular physiology more closely resembles that of man than does the dog. Their response (cardiovascular, metabolic, hormonal) to hemorrhage is entirely in keeping with what is known from other laboratory animals and man. Of passing note, we were not able to substantiate the claim of others (106) that the swine has high pulmonary artery pressure.

Our animals are undoubtedly not "at rest" as are those of Hannon (104-105). However, it is necessary to ventilate the awake normovolemic animals in order to conduct valid comparison of that state with the state following induction of anesthesia. Nevertheless, the awake normovolemic values for our swine appear to fall within the broad range of values reported by others for unanesthetized swine (104-110,129). Hannon (104) has discussed the possible reasons for data variability in the literature, and those need not be repeated here.

E. Conclusions:

The investigation is in progress; thus, conclusions are not possible.

F. Recommendations:

1. Swine should be considered for increased use for studies involving hemorrhage.

2. The study described in this report should be completed.

3. Studies should be initiated to delineate the mechanisms causing hypoperfusion with induction of anesthesia during hypovolemia. These investigations are likely to result in ability to improve casualty management of induction of anesthesia during hypovolemia.

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9. Tables

Table 1. Awake Swine Cardiovascular Response at 30% Blood Loss

Variable	Awake Blood Loss 0%	Awake Blood Loss 30%
Right atrial pressure, torr	2.0 ± 0.6	0.0 ± 0.4***
Pulmonary arterial wedge pressure, torr	2.4 ± 0.3	0.6 + 0.3****
Heart rate, beats/min	121 ± 9	179 ± 15****
Systemic vascular resistance, units	35.7 ± 1.4	48.0 ± 3.2***
Pulmonary vascular resistance, units	3.03 ± 0.16	4.45 ± 0.38****
Cardiac output, ml/min/kg	180 ± 7	101 ± 5****
Mean systemic arterial pressure, torr	131 ± 4	95 ± 7****
Mean pulmonary arterial pressure, torr	13.5 ± 0.5	9.7 ± 0.5****
Oxygen consumption, ml O_2/min/kg	8.45 ± 0.32	8.21 ± 0.35
Base-excess, mmol/liter	3.6 ± 0.6	1.1 ± 0.8***
Blood lactate, mmol/liter	1.5 ± 0.3	2.4 ± 0.3***
Plasma epinephrine, pg/ml	247 ± 32	1395 ± 362*
Plasma norepinephrine, pg/ml	137 ± 18	485 ± 212
Plasma renin activity, ng/ml	18.5 ± 2.5	41.1 ± 4.2***

n = 17; n = 7 for catecholamine concentrations and plasma renin activity.

*P < 0.05
**P < 0.01
***P < 0.005
****P < 0.001

10. Publications Supported by This Contract

1. Weiskopf RB, Townsley MI, Riordan KK, et al: Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane, and ketamine anesthesia. Anesth Analg 60:481-491, 1981

2. Weiskopf RB, Fairley HB: Anesthesia for major trauma. Surg Clin North Am, in press

3. Weiskopf RB, Townsley MI, Riordan KK, et al: Acid-base alignment and curve nomograms for swine blood. Scand J Clin Lab Invest, submitted

11. Personnel Receiving Support for This Contract

1. Weiskopf, Richard B., M.D.: Principal investigator
2. Montgomery, Sue: Staff Research Associate
3. DeManincor, Darlene: Staff Research Associate

12. Addenda

A. Problems:

Several problems have been encountered during this contract period.

1. A key piece of equipment was delayed in arrival (1 March 1981), and, thus, contract work could not begin until that date (as indicated in quarterly report #1, dated 30 December 1980).

2. Dogs became increasingly difficult to obtain, and thus the model was switched to swine (as indicated in quarterly report #1, dated 30 December 1980). Although swine have proven to be quite satisfactory, this did result in some additional delays (as indicated in quarterly report #3, dated 8 July 1981).

3. We occasionally continue to encounter some minor difficulty in obtaining swine of the proper weight for the experimental dates desired.

Acid-base curve and alignment nomograms for swine blood

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Running head: Acid-base nomograms for swine blood

Abstract

Weiskopf, R.B., Townsley, M.I., Riordan, K.K., Harris, D. and Chadwick, K. Acid-base curve and alignment nomograms for swine blood.

We constructed curve and alignment nomograms for acid-base status of swine blood. These nomograms differ from those constructed by Siggaard-Andersen for human blood. We reappraised the methodology for construction of the nomograms and discussed the possible reasons for the observed differences.

Key-words: All key words are in the title.

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In recent years, the pig has become increasingly popular as an experimental animal. To maintain "normal" values during some of our experiments [9], we needed to know the acid-base parameters of swine blood. We were unable to find this information in the literature. Although we lacked information indicating specific differences in acid-base parameters between human and experimental animal blood, we were not especially concerned until the report of Scott Emuakpor et al. [12], which indicated differences between human and canine blood in the hemoglobin-independent plot of log P_{CO_2} against pH. Those findings and our need to characterize the acid-base status of swine blood led to the present investigations. As a result, acid-base curve and alignment nomograms were constructed for swine blood, and the methodology used for their construction was reappraised.

MATERIALS AND METHODS

Collection and Handling of Blood

Four studies were performed; each study used the blood of a different pig. Each pig's blood was handled in a

similar fashion. Pigs were anesthetized with thiopental, and 330 ml of arterial blood was collected in heparin (33 units/ml blood). Whole blood was centrifuged and three red blood cell dilutions (aproximately 9, 27 and 45%) were prepared from the separated red blood cells and plasma. A sample of well-mixed original whole blood and samples of each dilution were placed in ice for later determination of total protein [6], hemoglobin [6], 2,3-diphosphoglycerate [8] and methemoglobin [3] concentration. Blood samples were prepared in duplicate at base excesses (BE) of -25, -20, -15, -10, -5, 0, +5, +10, +15 and +20 mEq/l at each of the three hemoglobin concentrations (a total of 60 samples) by adding 100 µl of working acid or base solution (see below) to 3.9 ml of blood. To prevent red cell lysis, blood samples were briefly centrifuged at low speed, and the acid or base solution was added to the swirling supernatant plasma. Samples were then gently but thoroughly mixed. Blood preparation was followed by tonometry and measurement of pH. One member of each pair of blood samples was equilibrated for 7 min in an Instrumentation Laboratories Model 213 tonometer with a

gas mixture of 2.72% CO_2 in O_2; the other member of the pair was similarly equilibrated with a gas mixture of 9.60% CO_2 in O_2. The gas mixtures had been previously analyzed in triplicate using the method of Scholander [11]. (When these gas flows and concentrations and blood volumes were used in preliminary experiments, equilibration of blood with CO_2 was achieved within 4-5 min.)

We measured pH using a Severinghaus-UC electrode [13] thermostatically controlled at 38.8°C, and a Lorenz Model 3 DBM-3 amplifier. The pH electrode was calibrated with precision reference buffers (pH 6.839 and 7.379 at 38.8°C, Radiometer, 3-ml sealed glass ampules). Electrode calibration was checked with the 7.379 buffer before and after each blood sample reading. Measurements were performed in duplicate with a maximal allowable difference between the two determinations of 0.003 pH units. The mean (± SD) of the difference between the paired reading for all samples, calculated without respect to sign, was 0.001 ± 0.001 pH units. Measurements of pH were corrected for red cell suspension

effect [17, 19]. Carbon dioxide partial pressure was measured in duplicate using a CO_2 electrode (Radiometer E5036) in a steel-and-glass cuvet (Radiometer D616) thermostatically controlled at 38.8°C. The electrode was calibrated with gas mixtures analyzed in triplicate using the method of Scholander [11]. A reading of a standard gas with a P_{CO_2} close to that expected for the blood sample was taken before and after each blood sample reading. Blood CO_2 tensions were systematically measured to ensure equilibration of blood with CO_2. Mean (± SD) difference between measured and expected blood P_{CO_2} (calculated without regard to sign) was 0.88 ± 0.27 mm Hg at P_{CO_2} of 67.9 mm Hg. Readings for pH and P_{CO_2} were corrected for electrode drift.

Preparation and Standardization of Acid and Base Solutions

A 1.0 N solution of Na_2CO_3 (100%, certified alkalimetric standard, Fischer Scientific Co.) was prepared and used to standardize, by titration, what we determined to be a stock solution of 1.01 N HCl. The 1.01 N

HCl was used as a titrant for a stock solution of what we determined to be 1.03 N $NaHCO_3$. Concentrations of 0.2 N, 0.4 N, 0.6 N and 0.8 N acid and base working solutions were prepared volumetrically from the stock solutions. All working solutions were titrated as described above. All titrations were repeated after completion of the bench laboratory work reported here; no differences were noted between determinations made before and after these experiments.

Data Analysis

The data generated for each pig resulted in three sets of values (one for each concentration of hemoglobin). Each set contained values for pH and P_{CO_2} for blood samples at each base excess (0 to 20 mEq/l of acid or base added). However, since the base excess of the blood drawn from the animal was not necessarily zero, the data was "normalized" to correct for any small acid-base imbalance at the time of sampling. To accomplish this, Siggaard-Andersen and Engel [20, 23] plotted constant CO_2 titration curves (pH vs. acid or base added) at both carbon dioxide tensions for each

hemoglobin concentration. They curve-fit their data by eye and hand, and similarly shifted the axis for the added acid or base so that zero corresponded to pH 7.400 for the P_{CO_2} 40 mm Hg curve [18]. In following their methodology, we noticed that minor differences in curve-fitting and shifting the data "by eye" resulted in relatively large differences in the final nomograms. Unable to arbitrarily resolve these observed differences, we used precise mathematical and graphical techniques which were implemented by a computer.

For each concentration of hemoglobin, we calculated regression coefficients using a forward stepwise (with a backward glance) selection procedure [5] to fit the model:

$$pH = (C_1+C_2*BE+C_3*BE^2+C_4*BE^3+C_5*BE^4)*\log P_{CO_2}+ C_6+C_7*BE+C_8*BE^2+C_9BE^3+C_{10}*BE^4$$

This model has the following properties: a) for any given BE the relationship between pH and log P_{CO_2} is linear; b) the slope and intercept of this relationship may vary non-linearly with BE; and c) for each

concentration of hemoglobin, the calculated coefficients define a model that fits the data with high statistical significance ($R^2 > 0.99$).

For each level of hemoglobin, the equation was "normalized" to a pH of 7.400 for a BE of zero and a P_{CO_2} of 40.0 mm Hg, based on the observations of Sawyer et al. [10] in awake mini-swine. This "normalization" was accomplished by solving each derived regression for BE at pH = 7.4 and P_{CO_2} = 40 mm Hg using the Jenkins-Traub three-stage logarithm [7]. The result, BE_{error}, represented the deviation of the acid-base status of the animal from zero at the time the blood was drawn. Values for the amount of acid or base added (BE) were then adjusted (shifted) by the amount of BE_{error}. The above regression model was then refit using the shifted BE values.

Curve Nomogram: Using the equations resulting from the above curve-fitting procedure, we calculated the relationship between pH and log P_{CO_2} for each of the three concentrations of hemoglobin at each level of BE. Siggaard-Andersen and Engel [23] stated that for each level of BE there exist a single pH and

P_{CO_2} that are independent of hemoglobin concentration. Therefore, for each level of BE, the three lines calculated above should intersect at a single point. Brodda [2] has calculated that this can only occur if shifts in water between the red blood cell and plasma that result from changes in pH are taken into account. Experimentally, the three isohemoglobin lines at each level of BE result in three intersections. Several approaches are possible when approximating the hemoglobin-independent point by computer. For example, the three points of intersection could be averaged. However, this method can be shown to be subject to large error when two of the hemoglobin lines are nearly parallel. Other simple methods of approximation are similarly subject to error. At the expense of being more complex and cumbersome, our approach avoided this potential error.

We approximated the hemoglobin-independent point by calculating the point which minimized the mean square difference in pH and in log P_{CO_2} between the point and the three buffer slope (isohemoglobin) lines. Intuitively, such a point would be the point requiring

the smallest change in the projection of the three hemoglobin lines in order to produce a common intersection. We derived this point in the following fashion.

Let $(pH_{ind}, \log P_{CO_2 ind})$ be the Hb-independent point.

Let m_i and b_i, $i = 1, 2, 3$ be the slopes and intercepts of the three linear relationships calculated from the regression model for a given BE (i.e., $pH = m_i \log P_{CO_2} + b_i$). Solve the following set of equations for pH_{ind} and $\log P_{CO_2}$ ind:

$$\frac{dX}{d(pH_{ind})} = 0$$

where $X = (pH_1 - pH_{ind})^2 + (pH_2 - pH_{ind})^2 + (pH_3 - pH_{ind})^2$

$$\frac{dY}{d(\log P_{CO_2 ind})} = 0$$

where $Y = (\log P_{CO_2 1} - \log P_{CO_2 ind})^2 + (\log P_{CO_2 2} - \log P_{CO_2 ind})^2 + (\log P_{CO_2 3} - \log P_{CO_2 ind})^2$

$$\left.\begin{aligned} pH_i &= m_i \log P_{CO_{2_{ind}}} + b_i \\ \log P_{CO_{2_i}} &= \frac{pH_{ind} - b_i}{m_i} \end{aligned}\right\} \quad \text{for } i = 1,2,3$$

A curve nomogram was then plotted by connecting the hemoglobin-independent points for a series of BE values.

Alignment nomogram: Curve-shifted data were used for a computerized construction of the alignment nomogram, in a manner similar to that described by Siggaard-Andersen [21].

"Mean" Pig

For each pig, the previously derived regression equations (one for each concentration of hemoglobin) were used to calculate pH values at each standard P_{CO_2}, at each standard base-excess. The resulting four pH values (one per pig) at each P_{CO_2}, BE and concentration of hemoglobin were averaged, thus producing a set of data representing the "mean" pig. Raw data could not be used for this purpose because the base-excess values of the sampled blood differed slightly among pigs, thus requiring differing degrees of "curve-

shifting" to achieve "normalization". "Mean" pig data were then handled as if they were from a single pig, and the above described analysis was performed. The result was separate "mean" curve and alignment nomograms.

RESULTS

The mean acid-base curve nomogram for swine blood is depicted in Fig. 1; the data are presented in Table I. We compared our curve nomogram for swine blood with that of Siggaard-Andersen [20] for human blood, and with that of Scott Emuakpor [12] for canine blood (Fig. 2). The alignment nomogram is shown in Fig. 3.

DISCUSSION

Our mean curve and alignment nomograms for swine blood are different from nomograms for human blood [20, 21] and canine blood [12] (Fig. 3). To compare the alignment nomogram with that drawn by Siggaard-Andersen for human blood [21], we plotted our data of known pH, P_{CO_2}, hemoglobin concentration and base-excess on the Siggaard-Andersen alignment nomogram as if we were unaware of the true base-excess value. The base-excess

values determined from the Siggaard-Andersen nomogram were compared with the true BE values. The resultant estimated base-excesses differed ($P<0.001$) from the known base-excess of all blood samples at all concentrations of hemoglobin and base-excess, except at a BE of zero, for which the results are definitionally identical. In nearly all cases, however, the calculated value was within $\pm$ 10% of the true value.

There are several possible explanations for the differences between our nomogram and that of Siggaard-Andersen. Neither set of data is based on the blood of a large population: Siggaard-Andersen used the blood of four people, we used four swine. However, in our experiments, individual variation did not appear to be an important problem.

Some of the observed differences may relate to differences in species. Scott Emuakpor et al. [12] described a curve nomogram for canine blood which differed from Siggaard-Andersen's curve nomogram for human blood. The buffer value of plasma proteins and hemoglobin can vary among mammalian species [4, 24], and this may account for some, but not all [22], of the

differences among the nomograms. Measured total protein of our swine blood (7.2 ± 0.3 g/dl) was similar to the normal value for man.

To create blood samples of altered base-excess, we avoided important dilution of plasma proteins by adding small amounts of relatively concentrated (0.2-0.8 N) acid or base. We thereby produced some alterations in ionic strength of blood, which may account for some of the differences between our nomograms for swine blood and those of Siggaard-Andersen for human blood [20, 21]. However, our curve nomogram for swine blood differs even more from the original curve nomogram of Siggaard-Andersen and Engel for human blood [23], for which the identical method of addition of acid or base was used.

To construct the nomograms, we followed the general methodology of Siggaard-Andersen. However, the two methodologies differ in several important ways.

We used a method different from that of Siggaard-Andersen to "shift" the original data in order to "normalize" the drawn blood to the established definition of BE = 0, pH 7.400, P_{CO_2} 40.0 mm Hg. Siggaard-

Andersen accomplished the following tasks graphically, fitting the curve and selecting the points by eye [18]: a) curve-fitting the two constant CO_2 titration curve plots (pH vs. acid or base added) at each concentration of Hb; b) estimating similar data for P_{CO_2} 40 mm Hg, assuming a linear relationship between log P_{CO_2} and pH, followed by curve-fitting of the P_{CO_2} 40 mm Hg data as in a); c) estimating the axis shift (acid or base added) to align the P_{CO_2} 40 mm Hg data so that at a pH of 7.400, base-excess was set equal to zero; d) estimating from the hand-drawn iso-P_{CO_2} curves, the pH at pre-selected levels of base-excess. We accomplished all of the above with a computer, the resulting curve-fit equations describing the data with an accuracy of more than 99.95%.

To draw the base-excess grid, Siggaard-Andersen used his previously developed pH-log P_{CO_2} curve nomogram for one set of blood pH and P_{CO_2} values, and an empirical relationship between buffer base, hemoglobin concentration and base-excess to estimate the required second pair of blood pH and P_{CO_2} values. Because of our uncertainties regarding the

specificity of the pH-log P_{CO_2} curve nomogram and the empirical relationship described above, we chose to use our original data and the computer-generated curve-fits to that data to determine the base-excess grid.

To generate the continuous isohemoglobin lines of the base-excess grid from the original data, we developed computerized empirical mathematical equations that were plotted by computer. Siggaard-Andersen used points determined graphically to draw curves by hand. Although we have not examined systematically the differences between the two techniques, we did note before completion of the computer programs that seemingly small, unimportant interpretive differences that occurred when drawing curves by hand through the original data created relatively large differences in the estimated amount required to shift the "acid-or-base-added" axis. These differences created relatively large differences in the alignment nomogram.

Another difference between Siggaard-Andersen's nomogram and our own is the temperature at which tonometry and measurement of pH were performed.

Siggaard-Andersen's experiments were performed at 38°C; ours were performed at 38.8°C (normal body temperature for swine). Siggaard-Andersen correctly stated that measurements performed at temperatures within ± 2°C of 38°C (the standard temperature of his nomogram) are "without any practically significant error" [21]. We temperature-corrected some of our pH and P_{CO_2} data from 38.8°C to 38.0°C, and then estimated base-excess from our nomogram. All estimates were within ± 0.1 mmol/l of the true value. Similarly, using established data for pK' and solubility of CO_2 in plasma [14], we determined that change in calculated plasma HCO_3^- between 38.0°C and 38.8°C was less than 0.1 mmol/l.

Finally, there are differences in the methodology of measuring pH, the major variable upon which these nomograms rest. As a result of advances in design and construction of pH electrode [13] and amplifier [16], our determinations of pH probably had less variability (0.001 ± 0.001 pH units, SD) than did the measurements of Siggaard-Andersen. Variations in the measurement of pH that are usually considered minor (e.g., 0.003 pH units) result in surprisingly large differences in the

final nomogram, because relatively small changes in the slope of nearly parallel lines greatly alters their point of intersection. Small variations in pH create the largest changes in the nomogram in the base-excess range of +10 to +25 mEq/l: the range in which our nomogram differs most from that of Siggaard-Andersen.

ACKNOWLEDGMENTS

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Table I. Swine base excess curve nomogram

Coordinates			Coordinates		
Base excess ($mEq \cdot l^{-1}$)	pH (Units)	P_{CO_2} (mm Hg)	Base excess ($mEq \cdot l^{-1}$)	pH (Units)	P_{CO_2} (mm Hg)
-20	7.145	19.7	0	7.400	40.0
-19	7.162	20.7	+1	7.412	40.6
-18	7.178	21.8	2	7.424	41.0
-17	7.194	22.9	3	7.436	41.4
-16	7.208	24.1	4	7.448	41.6
-15	7.223	25.2	+5	7.461	41.7
-14	7.236	26.3	6	7.474	41.8
-13	7.249	27.5	7	7.488	41.8
-12	7.262	28.6	8	7.502	41.6
-11	7.275	29.8	9	7.517	41.3
-10	7.287	30.9	+10	7.532	40.9
- 9	7.298	32.0	11	7.548	40.4
- 8	7.310	33.1	12	7.565	39.8
- 7	7.321	34.1	13	7.582	39.1
- 6	7.333	35.1	14	7.600	38.3
- 5	7.344	36.1	+15	7.618	37.4
- 4	4.355	37.0	16	7.637	36.4
- 3	7.36b	37.9	17	7.657	35.3
- 2	7.377	38.6	18	7.678	34.2
- 1	7.389	39.4	19	7.700	33.0
			+20	7.722	31.7

Figure Legends

Fig. 1. Mean swine acid-base curve nomogram. See text for derivation of "mean" values of four swine and construction of the nomogram.

Fig. 2. Comparison of our "mean" swine data (○---○) with the human data of Siggaard-Andersen (△---△) and the canine data of Scott Emuakpor (◐---◐).

Fig. 3. Mean swine acid-base alignment nomogram. See text for derivation of "mean" data and construction of the nomogram.

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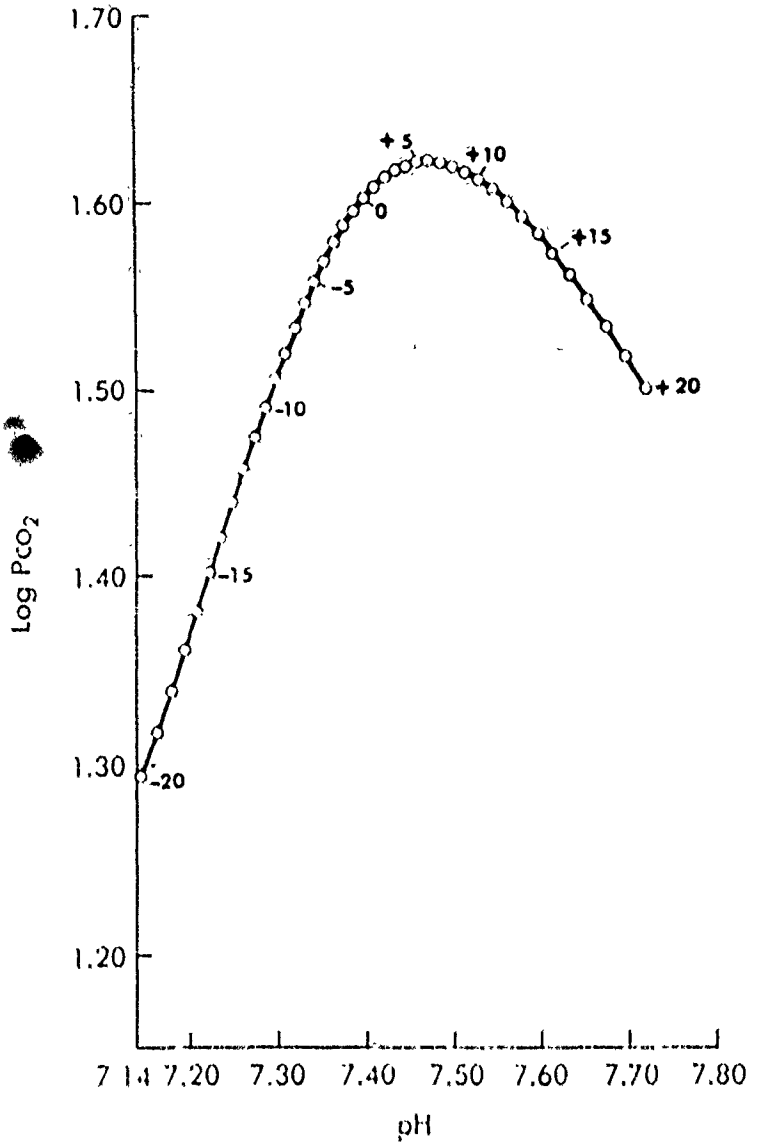
FIGURE 1


1.70
1.60
1.50
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Log P_{CO_2}
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pH

FIGURE 2

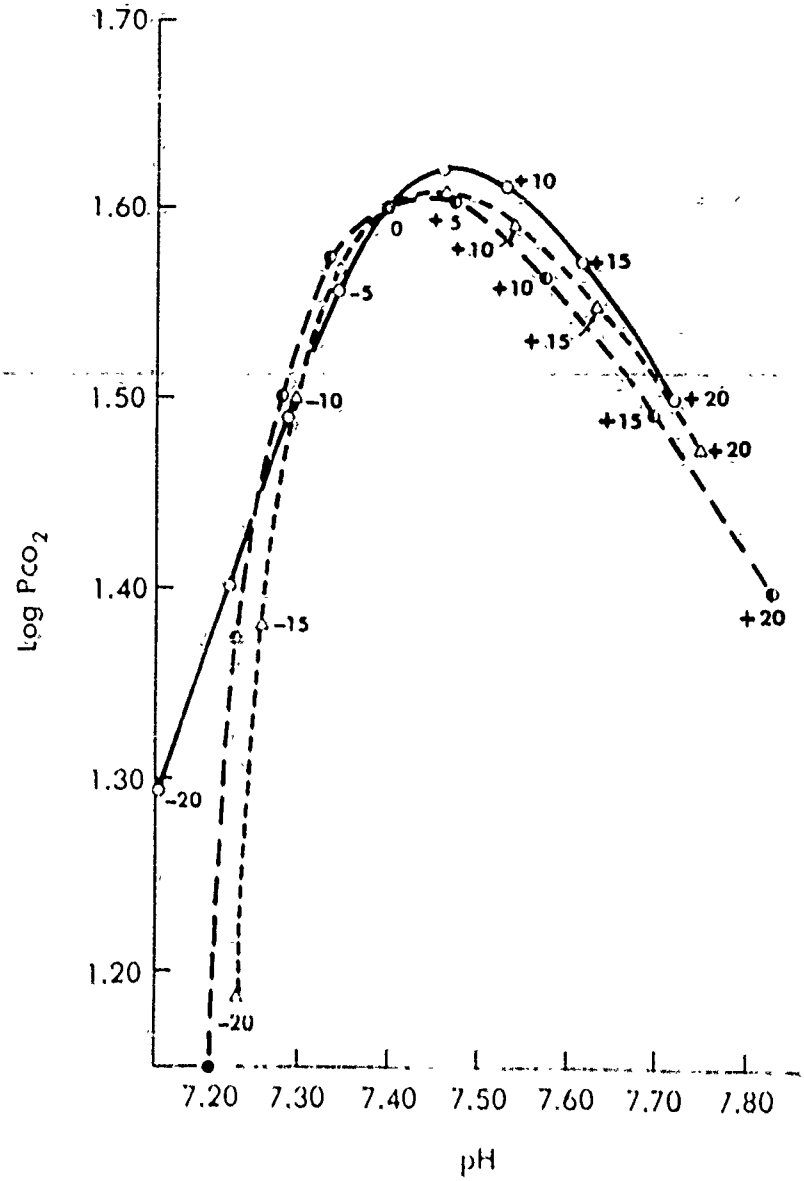
1.70
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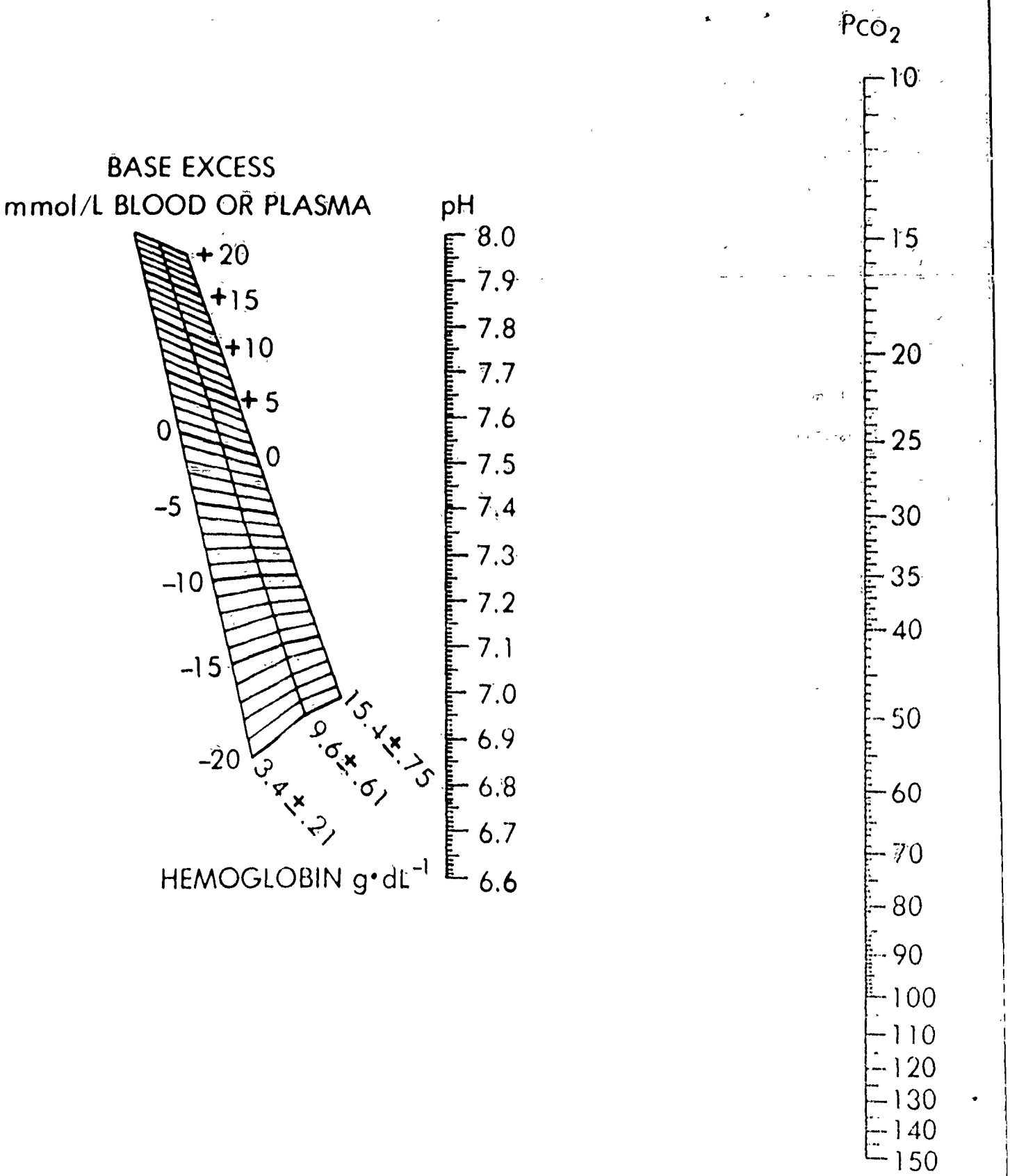
FIGURE 3


BASE EXCESS
mmol/L BLOOD OR PLASMA
+20
+15
+10
+5
0
-5
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-15
-20
15.4±.75
9.6±.61
3.4±.21
HEMOGLOBIN g·dL⁻¹
pH
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
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Comparison of Cardiopulmonary Responses to Graded Hemorrhage during Enflurane, Halothane, Isoflurane, and Ketamine Anesthesia

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WEISKOPF, R. B., TOWNSLEY, M. I., RIORDAN, K. K., CHADWICK, K., BAYSINGER, M., AND MAHONEY, E.: Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane, and ketamine anesthesia. Anesth Analg 1981;60:481-91.

To assess the influence of anesthetic agents during mild to moderate hemorrhage, the cardiopulmonary function of five awake, unmedicated dogs was compared with that during anesthesia with enflurane, halothane, isoflurane, and ketamine. Each dog was evaluated during anesthesia with each agent during normovolemia and after blood losses of 10%, 20%, and 30%. Before blood loss, in comparison with the awake state, ketamine increased heart rate (118 ± 11 beats/min, awake, vs 168 ± 17) and cardiac output (5.3 ± 0.4 L/min, awake, vs 6.0 ± 0.2). Halothane and isoflurane did not alter these variables. Enflurane decreased mean arterial blood pressure (110 ± 2 torr, awake, vs 72 ± 3), cardiac output (3.5 ± 0.1 L/min), and stroke volume (46 ± 4 ml, awake, vs 29 ± 2) to a greater extent than did the other anesthetics. Blood loss decreased cardiac output more with ketamine than with the inhalation anesthetics (ketamine, 0.120 L/min/percentage of blood loss; halothane, 0.077; isoflurane, 0.071; enflurane, 0.058; determined by least-squares linear regression, 0–30% blood loss), so that after 30% hemorrhage cardiac output was essentially the same during halothane (2.45 ± 0.19 L/min), isoflurane (2.83 ± 0.19 L/min), and ketamine (2.48 ± 0.15 L/min) anesthesia. Also, during hemorrhage, systemic vascular resistance increased most with ketamine; thus, after 30% blood loss, mean arterial blood pressure was highest with ketamine (ketamine, 94 ± 7 torr; enflurane, 48 ± 5 torr; halothane, 81 ± 4 torr; isoflurane, 58 ± 4 torr). Rate-pressure product and minute work were highest with ketamine throughout hemorrhage, except for minute work after 30% blood loss. These cardiovascular changes were reflected in the measurements of metabolism. Total body oxygen consumption ($\dot{V}_{O_2}$) was highest with ketamine after 0% to 20% blood loss (e.g., after 0% blood loss: ketamine, 8.6 ± 1.2 ml of O_2/min/kg; enflurane, 4.5 ± 0.5; halothane, 4.0 ± 0.3; isoflurane, 4.9 ± 0.6). During blood loss, $\dot{V}_{O_2}$ did not change with any inhalation anesthetic, but decreased with ketamine (6.0 ± 0.5 ml of O_2/min/kg after 30% blood loss); this decrease was associated with an increase in arterial blood lactate concentration and base deficit (ketamine, BE −8.0 ± 0.5 meq/L after 30% blood loss), suggesting that oxygen demand was not met during hypovolemia with ketamine anesthesia. In contrast, lack of change in blood lactate, base deficit, or oxygen consumption during hemorrhage with the inhalation anesthetics suggests that oxygen demand was satisfied when the dogs were bled during enflurane, halothane, or isoflurane anesthesia.

Key Words: ACID-BASE EQUILIBRIUM; ANESTHETICS, Intravenous: ketamine; ANESTHETICS, Volatile: enflurane, halothane, isoflurane; HEMORRHAGE: anesthetics, effects of; METABOLISM: lactate.

HEMORRHAGE stimulates the sympathoadrenal system. Anesthetic agents also may inhibit, stimulate, or have little influence on this system during normovolemia. It is not obvious whether additional stimulation, no effect, or inhibition of the sympathetic system would be most beneficial in anesthetized hypovolemic patients. Hemorrhage has been the subject of many investigations, most using one of the standard "shock" models, in which an experimental

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animal is bled to and maintained at a predetermined arterial blood pressure. Few investigations have used graded, measured hemorrhage as the independent variable.

Although a few limited studies of hemorrhage have used awake human volunteers (1), and some studies have used awake, restrained animals (2), most investigations have used anesthetized animals. These studies usually used injectable anesthetic agents, resulting in varying anesthetic depth during the course of the experiment. When an inhalational anesthetic agent was used, induction of anesthesia was usually accomplished with an injectable anesthetic, or constant end-tidal concentrations were not maintained, resulting in uncertain depth of anesthesia. When the influence of anesthetic agents on hemorrhage has been investigated, failure to remove the spleens of the experimental dogs (3–7) could have allowed uncontrolled and unquantified "autotransfusion" of as much as 35% of the shed blood (8).

Only Theye et al (7) compared in a single study the influence of three anesthetic anesthetics (cyclopropane, halothane, and isoflurane) on cardiovascular function during, and the metabolic consequences of, equivalent graded hemorrhage in dogs. Because they used survival times as their end point, comparing the effects of different anesthetics in the same animal was not possible. They did not remove the spleens, nor did they compare results during hemorrhage with those of awake, unmedicated dogs.

In the present report we have assessed, in hypovolemic dogs in which spleens had been removed, the benefits and disadvantages associated with the administration of anesthetics with differing effects on the sympathetic system. Ketamine, an anesthetic with stimulant-like properties that is frequently recommended for clinical use during hypovolemia, was compared with halothane, which likely inhibits release and activity of catecholamines (9, 10), and with enflurane and isoflurane.

Methods and Materials

We removed the spleens from five healthy mongrel dogs (25 to 32 kg each), previously trained to lie quietly in the laboratory, and provided them with chronic tracheostomies and exteriorized carotid arteries. A minimum of 2 weeks intervened between surgery and the studies. All animals were in good health for each study. All dogs were studied (in random order, separated by a minimum of 2 weeks between successive studies) awake or with 1.15 MAC of the inhalation anesthetics, or with a continuous infusion of ketamine. All animals breathed spontaneously at all times.

For the studies with inhalation anesthetics, the dogs were connected to a circle breathing circuit through a cuffed tracheostomy tube and a non-rebreathing Rudolph valve. Animals received no premedication. Anesthesia for the studies of halothane, enflurane, or isoflurane was induced with the agent to be studied, and was maintained at a constant end-tidal concentration of 1.00% halothane, 2.50% enflurane, or 1.69% isoflurane. The anesthetics were always delivered in a mixture of oxygen and nitrogen that was adjusted to maintain Pa_{O_2} close to 100 torr.

For the studies with ketamine, anesthesia was induced intravenously with 5.0 mg/kg of ketamine, and was maintained by a continuous infusion of ketamine in the smallest amount necessary to prevent gross movement (mean ± SE, 0.25 ± 0.03 mg/kg/min). After the induction of anesthesia, carotid and pulmonary arterial catheters were inserted percutaneously, and the dog was placed in the left lateral decubitus position.

For the awake studies, animals were first anesthetized with thiopental, 7.0 mg/kg; anesthesia was maintained with 70% N_2O in O_2 to allow for placement of carotid and pulmonary arterial catheters. No additional thiopental was administered, and N_2O was discontinued. Animals were studied at least 2 hours after awakening, at which time resting $Paco_2$ did not differ from $Paco_2$ measured on another occasion before administration of anesthetics or other drugs.

Ventilation was measured by using the rebreathing bag in the circle breathing system as a bag-in-a-box connected to a wedge spirometer (model 570, Med-Science Electronics, Inc). We continuously measured Po_2, Pco_2, and the partial pressure of halothane, enflurane, or isoflurane at the tracheostomy tube orifice by mass spectroscopy (Perkin-Elmer, model MGA 1100A) (11) (Townsley MI, Brinks HA, Weiskopf RB. Measurement of enflurane and isoflurane by mass spectrometry. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, October 21–25, 1978, Chicago, Illinois, pp 289–90). Carotid and pulmonary arterial pressures were measured by transducers (Statham 23 Db). Mean systemic and pulmonary arterial pressures were derived by a Brush recorder preamplifier. Cardiac output was estimated using a thermodilution technique, a thermistor-tipped pulmonary arterial catheter (Edwards Laboratories), and an analog computer (Gould, model SP1425). Cardiac output measurements were repeated until two successive measurements displaying satis-

factory washout curves differed by no more than 0.2 L/min. This usually occurred within two or three measurements. These physiologic parameters and the partial pressures of the measured gases and vapors were recorded graphically (Gould Brush, model 200, eight-channel polygraph) and magnetically (Hewlett-Packard, model 8868A FM tape recorder). Systemic vascular resistance was calculated as mean systemic blood pressure divided by cardiac output. Pulmonary vascular resistance was calculated as the difference between mean pulmonary artery pressure (PAP) and pulmonary artery wedge pressure divided by cardiac output. Left ventricular stroke work (LVSW) was calculated as the product of mean systolic blood pressure and stroke volume. Left ventricular minute work (LVMW) was calculated as the product of LVSW and heart rate.

Circulatory and ventilatory variables were measured during normovolemia and after 10%, 20%, and 30% reductions in the animal's estimated blood volume (12). Each dog's temperature, measured in the pulmonary arterial blood, was maintained within 1 C of its initial value by the use of circulating water heating pads.

Successive 10% reductions in blood volume were accomplished by drawing blood through the carotid arterial cannula over a period of approximately 10 minutes. The blood was collected into sterile, 600-ml transfer packs containing heparin, so that the final concentration was 3 units of heparin per milliliter of blood. At least 10 minutes of stability was allowed after each reduction in blood volume before beginning measurements at that level of oligemia. Following studies at 30% blood loss, the collected blood was transfused through a microfilter (Pall SQ40SK Ultipor blood transfusion filter); 20 minutes later all measurements were repeated and compared with values obtained before hemorrhage.

During each of the experimental conditions, Pa_{O_2} and Pa_{CO_2} were measured by Radiometer electrodes in steel and glass cuvets; pH was measured by a Severinghaus-UC electrode (13). All electrodes were maintained at 37 C. Calibrating gases and buffers were measured before and after each blood sample reading; the measurement was corrected for electrode drift, liquid-gas factor (14, 15), and the dog's temperature (16). Oxygen concentrations of systemic arterial (Ca_{O_2}) and pulmonary arterial ($C\bar{v}_{O_2}$) blood were measured in duplicate by a galvanic cell instrument (Lex-O_2-Con-TL, Lexington Instruments) (17). Base excess was estimated using a modification of the equations of Severinghaus (18).

During each condition, arterial blood samples were obtained for enzymatic measurement of whole blood lactate concentrations (19).

Results in the normovolemic anesthetized state were compared with results in the awake condition by analysis of variance with repeated measures and by Student's *t*-test for paired data. For each anesthetic, the influence of hemorrhage on the measured and calculated variables was assessed by analysis of variance with repeated measures. Comparison among anesthetic agents at normovolemia and at each level of hemorrhage was accomplished by analysis of variance with repeated measures and by Newman-Keuls method of multiple comparisons. Data obtained in normovolemic, anesthetized state after the return of shed blood were compared with data obtained before hemorrhage using the paired Student's *t*-test (20). In all cases, $p < 0.05$ was considered statistically significant.

As a control, all animals were anesthetized with ketamine for a second time; the same induction and maintenance doses were used. Although no hemorrhage was instituted, all other procedures and measurements were the same as in the first ketamine experiment, including the times at which measurements were performed. Statistical analysis of these data did not indicate significant change in any measured variable with time during ketamine anesthesia.

Results

Awake vs Anesthetized States (during Normovolemia)

Mean (±SE) values for the five normovolemic dogs are presented in Table 1.

All inhalation anesthetics decreased mean arterial blood pressure ($\bar{B}Pa$). The increase in $\bar{B}Pa$ observed during ketamine anesthesia was not statistically significant. During normovolemia, $\bar{B}Pa$ was higher with ketamine than with halothane, which was higher than with isoflurane, which was higher than with enflurane.

Cardiac output ($\dot{Q}$) decreased with enflurane, increased with ketamine, and did not change with halothane or isoflurane. During normovolemia, $\dot{Q}$ was higher with ketamine than with all inhalation anesthetics, and significantly lower with enflurane than with all other agents.

Only ketamine altered (increased) heart rate. Left ventricular stroke volume decreased only with enflurane, and during normovolemia it was higher with

TABLE 1

Comparison of Cardiorespiratory Responses of Five Dogs, Awake and Anesthetized, during Zero Blood Loss*

	Awake	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	0.0	2.48 ± 0.03	0.99 ± 0.01	1.68 ± 0.01	NA
$\overline{BP}a$ (torr)	109.6 ± 2.1	71.8 ± 3.3[d]	99.4 ± 2.3[a]	83.0 ± 7.0[a]	124.0 ± 6.6
HR (beats/min)	118.4 ± 10.8	117.8 ± 2.8	116.0 ± 5.8	125.0 ± 5.5	167.6 ± 17.4[a]
Q (L/min)	5.29 ± 0.35	3.45 ± 0.14[c]	4.80 ± 0.18	5.00 ± 0.20	5.97 ± 0.18[a]
SV (ml)	45.6 ± 3.5	29.4 ± 1.6[a]	41.8 ± 2.6	40.1 ± 0.7	37.5 ± 4.8
LVSW (g × m)	5.31 ± 0.47	2.25 ± 0.21[b]	4.41 ± 0.37	3.41 ± 0.31[b]	4.92 ± 0.66
LVMW (g × m/min)	611 ± 37	263 ± 19[b]	506 ± 30	421 ± 27[b]	783 ± 44[c]
SVR (torr/L/min)	21.2 ± 1.8	21.0 ± 1.1	20.8 ± 0.5	16.8 ± 1.8	20.8 ± 1.4
$\overline{PAP}$ (torr)	11.2 ± 2.0	14.3 ± 1.4	14.7 ± 1.8	14.5 ± 1.4	14.0 ± 1.6
PVR (torr/L/min)	1.09 ± 0.14	1.62 ± 0.22	1.52 ± 0.18	1.58 ± 0.39	1.85 ± 0.21
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	4.2 ± 0.29	3.8 ± 0.35	2.2 ± 0.17[a]	2.8 ± 0.22[b]	4.2 ± 0.53
$\dot{V}_{O_2}$ (ml O_2/min/kg)	7.73 ± 0.48	4.46 ± 0.52[a]	3.95 ± 0.32[d]	4.92 ± 0.55[a]	8.55 ± 1.17
T_{O_2} (ml O_2/min/kg)	32.7 ± 2.4	20.1 ± 1.6[c]	29.7 ± 0.8	29.4 ± 2.0[a]	36.8 ± 1.2
$T_{O_2}/\dot{V}_{O_2}$	4.26 ± 0.28	4.65 ± 0.43	7.76 ± 0.52[b]	6.14 ± 0.49[b]	4.58 ± 0.53
Pa_{O_2} (torr)	97.8 ± 3.8	109.8 ± 3.7[a]	95.9 ± 1.0	107.9 ± 5.2	123.6 ± 8.4
Pa_{CO_2} (torr)	31.3 ± 1.5	49.3 ± 2.8[c]	42.0 ± 2.3[a]	56.2 ± 2.3[b]	32.4 ± 0.9
pHa	7.439 ± 0.011	7.298 ± 0.018[b]	7.336 ± 0.010[b]	7.230 ± 0.022[b]	7.416 ± 0.015
BE (meq/L)	−3.3 ± 0.6	−2.4 ± 0.7	−3.4 ± 1.1	−3.9 ± 0.9	−3.9 ± 0.7
Hct (%)	38.1 ± 0.6	39.3 ± 0.6[a]	38.7 ± 0.5	38.3 ± 1.5	38.8 ± 1.3
Lactate (mM/L)	1.39 ± 0.14	0.33 ± 0.09[b]	1.83 ± 0.28	0.86 ± 0.11[a]	1.75 ± 0.41
PAPw (torr)	5.5 ± 1.7	8.7 ± 1.4	7.1 ± 2.2	7.6 ± 2.5	5.3 ± 1.0
RPP (× 10^3)	16.8 ± 1.1	11.0 ± 0.3[a]	14.5 ± 0.8	13.9 ± 1.2	28.3 ± 2.8[a]
$\dot{V}_E$ (L/min)		3.8 ± 0.5	5.8 ± 0.9	5.7 ± 1.9	14.5 ± 1.1
f, (breaths/min)		9.0 ± 1.8	19.2 ± 4.9	21.9 ± 12.4	39.7 ± 4.4
V_T (L)		0.47 ± 0.04	0.32 ± 0.03	0.37 ± 0.05	0.38 ± 0.06

* Values are means ± SE of five dogs. Abbreviations used are: $\overline{BP}a$, mean arterial blood pressure; HR, heart rate; Q, cardiac output; SV, stroke volume; LVSW, left ventricular stroke work; LVMW, left ventricular minute work; SVR, systemic vascular resistance; $\overline{PAP}$, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; $C(a\text{-}\bar{v})_{O_2}$, arterial-venous oxygen concentration difference; $\dot{V}_{O_2}$, total body oxygen consumption; T_{O_2}, oxygen transport; Pa_{O_2}, partial pressure of oxygen in arterial blood; Pa_{CO_2}, partial pressure of carbon dioxide in arterial blood; pHa, arterial blood pH; BE, base excess of arterial blood; Hct, hematocrit; PAPw, pulmonary arterial wedge pressure, RPP, rate-pressure product; $\dot{V}_E$, expired minute ventilation; f, respiratory frequency; V_T, tidal volume; NA, not applicable. Comparison of responses produced by each anesthetic separately with awake state. [c]$p < 0.05$, [b]$p < 0.01$, [a]$p < 0.005$, and [d]$p < 0.001$. For other statistical information, see Tables 5 and 6.

isoflurane and halothane than with ketamine and enflurane.

LVSWork decreased with isoflurane, and to a greater extent with enflurane. Ketamine and halothane did not alter LVSW; consequently, LVSW was lower with enflurane than with the three other anesthetic agents. Similarly, LVMW declined with enflurane and isoflurane, but increased with ketamine as a result of increased heart rate. Consequently, during normovolemia, LVMW was greater with ketamine than with the three other anesthetics, whereas LVMW was lower with enflurane than with the three other anesthetics.

None of the four agents altered peripheral or pulmonary vascular resistances or mean pulmonary arterial or pulmonary wedge pressures.

Total body oxygen consumption ($\dot{V}_{O_2}$) decreased with all three inhalation anesthetics and did not change with ketamime. Consequently, during normovolemia, $\dot{V}_{O_2}$ was higher with ketamine than with all three inhalation anesthetics. The ratio of oxygen transported to oxygen consumed ($T_{O_2}/\dot{V}_{O_2}$) increased with halothane and isoflurane, but did not change with either ketamine or enflurane. During normovolemia, $T_{O_2}/\dot{V}_{O_2}$ was higher with halothane than with all other agents, and was higher with isoflurane than with either enflurane or ketamine.

None of the anesthetics altered base excess. Blood lactate concentrations decreased significantly with enflurane and isoflurane and did not change with halothane and ketamine. There were no differences among blood lactate concentrations for these anesthetic agents during normovolemia.

Physiologic Sequelae of Hemorrhage

Cardiopulmonary responses to the four anesthetic agents during 10%, 20%, and 30% blood loss are shown in Tables 2, 3, and 4, respectively; statistical

TABLE 2

Cardiorespiratory Responses of Five Anesthetized Dogs during 10% Blood Loss*

	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	2.49 ± 0.04	1.00 ± 0.01	1.72 ± 0.02	NA
$\overline{BP}$a (torr)	69.6 ± 2.6	91.8 ± 3.3	77.8 ± 4.4	124.0 ± 5.6
HR (beats/min)	117.4 ± 2.9	104.6 ± 5.3	120.2 ± 2.7	177.8 ± 17.6
$\dot{Q}$ (L/min)	2.92 ± 0.10	3.74 ± 0.08	4.15 ± 0.12	5.11 ± 0.39
SV (ml)	23.8 ± 0.4	36.0 ± 1.7	34.6 ± 1.3	29.8 ± 3.1
LVSW (g × m)	1.74 ± 0.07	3.51 ± 0.28	2.86 ± 0.23	3.66 ± 0.35
LVMW (g × m/min)	215 ± 15	362 ± 15	343 ± 26	672 ± 58
$\overline{SVR}$ (torr/L/min)	23.8 ± 0.7	24.6 ± 1.1	18.7 ± 0.9	24.7 ± 2.0
$\overline{PAP}$ (torr)	12.3 ± 1.3	11.7 ± 1.9	11.9 ± 1.0	11.6 ± 1.9
PVR (torr/L/min)	1.94 ± 0.33	1.47 ± 0.28	1.75 ± 0.26	1.82 ± 0.07
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	4.4 ± 0.48	3.4 ± 0.14	3.7 ± 0.37	6.0 ± 0.70
$\dot{V}_{O_2}$ (ml O_2/min/kg)	4.39 ± 0.61	4.70 ± 0.12	5.40 ± 0.53	10.53 ± 1.24
T_{O_2} (ml O_2/min/kg)	16.4 ± 1.6	23.1 ± 0.6	23.0 ± 1.1	31.2 ± 1.9
$T_{O_2}/\dot{V}_{O_2}$	3.92 ± 0.43	4.93 ± 0.17	4.42 ± 0.50	3.08 ± 0.28
Pa_{O_2} (torr)	110.9 ± 5.5	96.9 ± 3.4	105.4 ± 2.6	123.1 ± 5.7
Pa_{CO_2} (torr)	45.2 ± 1.8	42.4 ± 2.1	54.5 ± 3.2	30.0 ± 1.4
pHa	7.328 ± 0.010	7.329 ± 0.012	7.230 ± 0.027	7.401 ± 0.020
BE (meq/L)	−2.5 ± 0.6	−3.9 ± 1.0	−4.9 ± 0.6	−5.5 ± 1.1
Hct (%)	38.3 ± 0.6	37.1 ± 0.9	36.4 ± 1.0	37.8 ± 1.1
Lactate (mM/L)	0.34 ± 0.10	1.87 ± 0.24	0.88 ± 0.14	2.57 ± 0.43
PAPw (torr)	6.6 ± 1.6	6.3 ± 1.8	5.2 ± 2.1	5.1 ± 1.0
RPP (× 10^3)	10.4 ± 0.3	12.1 ± 0.5	12.4 ± 0.8	30.5 ± 4.1
$\dot{V}_L$ (L/min)	5.1 ± 0.4	5.1 ± 0.6	4.7 ± 0.9	15.0 ± 1.9
f (breaths/min)	12.0 ± 0.9	15.7 ± 3.9	14.5 ± 5.5	48.2 ± 10.2
V_T (L)	0.43 ± 0.03	0.30 ± 0.02	0.39 ± 0.05	0.34 ± 0.04

* Values are means ± SE. Abbreviations are defined in footnote to Table 1. For statistical information, see Tables 5 and 6

TABLE 3

Cardiorespiratory Responses of Five Anesthetized Dogs during 20% Blood Loss*

	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	2.52 ± 0.02	1.02 ± 0.01	1.69 ± 0.02	NA
$\overline{BP}$a (torr)	61.8 ± 3.4	88.8 ± 2.8	69.0 ± 3.3	112.4 ± 7.9
HR (beats/min)	119.6 ± 4.2	113.8 ± 8.9	120.8 ± 4.3	190.2 ± 27.0
$\dot{Q}$ (L/min)	2.38 ± 0.14	3.10 ± 0.14	3.52 ± 0.13	3.58 ± 0.27
SV (ml)	19.9 ± 1.1	27.8 ± 1.9	29.2 ± 1.2	20.2 ± 3.0
LVSW (g × m)	1.31 ± 0.14	2.62 ± 0.25	2.13 ± 0.13	2.61 ± 0.51
LVMW (g × m/min)	157 ± 18	290 ± 11	256 ± 12	468 ± 90
$\overline{SVR}$ (torr/L/min)	26.2 ± 1.4	29.0 ± 1.9	19.8 ± 1.4	32.6 ± 2.3
$\overline{PAP}$ (torr)	10.6 ± 1.2	10.0 ± 1.4	9.2 ± 1.5	9.2 ± 2.1
PVR (torr/L/min)	1.87 ± 0.31	2.36 ± 0.22	1.68 ± 0.18	1.99 ± 0.82
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	5.9 ± 0.50	4.0 ± 0.34	4.2 ± 0.21	6.4 ± 0.48
$\dot{V}_{O_2}$ (ml O_2/min/kg)	4.74 ± 0.41	4.49 ± 0.22	5.22 ± 0.44	8.05 ± 1.41
T_{O_2} (ml O_2/min/kg)	13.2 ± 1.5	18.4 ± 0.9	19.0 ± 1.0	20.2 ± 2.4
$T_{O_2}/\dot{V}_{O_2}$	2.82 ± 0.31	4.15 ± 0.33	3.70 ± 0.25	2.69 ± 0.24
Pa_{O_2} (torr)	104.2 ± 3.2	99.5 ± 6.3	103.0 ± 2.9	118.8 ± 7.2
Pa_{CO_2} (torr)	43.4 ± 1.5	42.9 ± 2.3	56.7 ± 3.4	32.2 ± 1.3
pHa	7.340 ± 0.011	7.321 ± 0.013	7.221 ± 0.032	7.361 ± 0.011
BE (meq/L)	−2.6 ± 0.5	−4.5 ± 0.9	−4.7 ± 0.8	−7.4 ± 0.8
Hct (%)	36.7 ± 1.2	36.4 ± 1.0	36.3 ± 0.9	36.0 ± 1.0
Lactate (mM/L)	0.43 ± 0.13	1.68 ± 0.24	0.96 ± 0.12	2.76 ± 0.66
PAPw (torr)	5.8 ± 1.6	2.9 ± 1.2	3.6 ± 1.8	6.1 ± 2.1
RPP (× 10^3)	9.6 ± 0.6	12.6 ± 0.4	11.4 ± 0.6	29.4 ± 5.7
$\dot{V}_L$ (L/min)	6.1 ± 1.2	6.8 ± 1.2	5.1 ± 1.0	12.1 ± 2.3
f (breaths/min)	16.7 ± 5.1	19.2 ± 5.2	16.9 ± 6.3	36.8 ± 5.9
V_T (L)	0.39 ± 0.04	0.33 ± 0.02	0.37 ± 0.05	0.33 ± 0.19

* Values are means ± SE. Abbreviations are defined in footnote to Table 1. For statistical information, see Tables 5 and 6

TABLE 4

Cardiorespiratory Responses of Five Anesthetized Dogs during 30% Blood Loss*

	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	2.52 ± 0.02	0.98 ± 0.01	1.67 ± 0.02	NA
$\overline{BP}a$ (torr)	48.0 ± 4.8	81.0 ± 3.5	58.0 ± 4.0	94.0 ± 7.2
HR (beats/min)	120.0 ± 5.5	121.0 ± 10.7	124.2 ± 4.4	166.0 ± 11.8
$\dot{Q}$ (L/min)	1.69 ± 0.14	2.45 ± 0.19	2.83 ± 0.19	2.48 ± 0.15
SV (ml)	14.0 ± 0.9	20.7 ± 1.9	24.2 ± 1.2	15.4 ± 2.1
LVSW (g × m)	0.72 ± 0.11	1.79 ± 0.21	1.48 ± 0.10	1.74 ± 0.32
LVMW (g × m/min)	87.7 ± 15.5	208 ± 14	185 ± 14	288 ± 50
$\overline{SVR}$ (torr/L/min)	28.7 ± 2.4	34.0 ± 3.2	21.0 ± 2.4	38.4 ± 3.2
$\overline{PAP}$ (torr)	9.0 ± 0.9	7.6 ± 1.4	6.9 ± 1.8	6.0 ± 1.9
PVR (torr/L/min)	2.89 ± 0.35	2.06 ± 0.26	1.52 ± 0.40	1.98 ± 0.88
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	8.1 ± 0.79	5.5 ± 0.53	5.0 ± 0.58	7.5 ± 1.09
$\dot{V}_{O_2}$ (ml O_2/min/kg)	4.48 ± 0.31	4.82 ± 0.23	4.88 ± 0.19	5.99 ± 0.54
T_{O_2} (ml O_2/min/kg)	9.03 ± 1.34	13.5 ± 0.7	14.1 ± 1.1	12.4 ± 1.0
$T_{O_2}/\dot{V}_{O_2}$	2.00 ± 0.25	2.90 ± 0.24	2.92 ± 0.28	2.17 ± 0.40
Pa_{O_2} (torr)	108.4 ± 3.0	100.0 ± 7.1	102.3 ± 5.2	118.0 ± 10.6
Pa_{CO_2} (torr)	41.9 ± 2.6	42.4 ± 2.1	54.3 ± 3.5	33.3 ± 2.8
pHa	7.345 ± 0.024	7.315 ± 0.011	7.224 ± 0.029	7.336 ± 0.018
BE (meq/L)	−3.4 ± 0.5	−4.7 ± 0.8	−5.7 ± 0.6	−8.0 ± 0.5
Hct (%)	36.3 ± 0.9	36.0 ± 1.7	34.5 ± 0.9	33.0 ± 0.5
Lactate (mM/L)	0.45 ± 0.13	1.79 ± 0.35	0.93 ± 0.17	3.13 ± 0.46
PAPw (torr)	4.0 ± 1.2	2.6 ± 1.2	3.1 ± 1.8	3.8 ± 1.5
RPP ($\times 10^3$)	7.7 ± 0.9	11.9 ± 0.6	9.6 ± 0.6	21.2 ± 3.5
$\dot{V}_E$ (L/min)	7.3 ± 2.9	7.2 ± 1.4	6.3 ± 1.6	10.9 ± 0.9
f (breaths/min)	24.9 ± 13.6	19.2 ± 5.4	21.3 ± 8.5	33.4 ± 6.2
V_T (L)	0.37 ± 0.05	0.39 ± 0.10	0.37 ± 0.05	0.35 ± 0.04

* Values are means ± SE. Abbreviations are defined in footnote to Table 1. For statistical information, see Tables 5 and 6.

analyses of the effects of hemorrhage on each variable are given in Table 5.

Progressive hemorrhage decreased left-sided filling pressure (pulmonary arterial wedge pressure) with the inhalation anesthetics but not with ketamine; stroke volume decreased with all agents. Heart rate did not change with hemorrhage with any anesthetic agent; consequently, $\dot{Q}$ decreased progressively with graded hemorrhage with all agents. Systemic vascular resistance (SVR) increased progressively during graded hemorrhage with all agents but insufficiently to prevent a progressive decrease in $\overline{BP}a$, which occurred with all agents. Similarly, pulmonary vascular resistance increased during blood loss with halothane and enflurane, but did not change with ketamine and isoflurane. Mean pulmonary arterial pressure decreased progressively with hemorrhage with each anesthetic agent.

As $\overline{BP}a$ decreased without alteration in heart rate, both stroke work and minute work progressively decreased during graded hemorrhage with all anesthetics. However, rate-pressure product decreased with the inhalation anesthetics with blood loss, but decreased with ketamine only at the 30% level.

As $\dot{Q}$ progressively decreased with graded hemorrhage, tissue oxygen extraction [arterial-mixed venous oxygen concentration difference, $C(a\text{-}\bar{v})O_2$] increased with all agents. This compensation was adequate with the inhalation anesthetics, but not with ketamine; oxygen consumption did not change with blood loss with the inhalation anesthetics, but decreased with ketamine. Oxygen transport decreased with hemorrhage with all agents, as did $T_{O_2}/\dot{V}_{O_2}$.

Base deficit increased with blood loss with all agents except enflurane. Hemorrhage did not change blood lactate concentrations with the inhalation anesthetics, blood lactate concentrations increased with hemorrhage with ketamine.

No ventilatory measurement (expired minute ventilation, ventilatory frequency, or tidal volume) changed with hemorrhage with any anesthetic. Hematocrit did not change during hemorrhage with halothane or ketamine, but decreased slightly with enflurane and isoflurane.

Comparison among Anesthetic Agents of Physiologic Sequelae of Hemorrhage

Statistical analysis of comparison among anesthetic agents at each level of hemorrhage is presented in Table 6.

TABLE 5
Statistical Analysis of Physiologic Sequelae of Hemorrhage in Five Anesthetized Dogs*

	Enflurane	Halothane	Isoflurane	Ketamine
$\overline{BP}a$	0.001	0.001	0.001	0.001
HR	NS	NS	NS	NS
$\dot{Q}$	0.001	0.001	0.001	0.001
SV	NS	0.001	0.001	0.001
LVSW	0.001	0.001	0.001	0.001
LVMW	0.001	0.001	0.001	0.001
$\overline{SVR}$	0.01	0.001	0.05	0.001
$\overline{PAP}$	0.001	0.001	0.001	0.001
PVR	0.001	0.05	NS	NS
$C(a\text{-}\bar{v})_{O_2}$	0.001	0.001	NS	NS
$\dot{V}_{O_2}$	NS	NS	NS	0.05
T_{O_2}	0.001	0.001	0.001	0.001
$T_{O_2}/\dot{V}_{O_2}$	0.001	0.001	0.001	0.01
Pa_{O_2}	NS	NS	NS	NS
Pa_{CO_2}	NS	NS	NS	NS
pHa	NS	NS	NS	NS
BE	NS	0.05	0.05	0.01
Hct	0.01	NS	0.01	NS
Lactate	NS	NS	NS	0.01
PAPw	0.001	0.05	0.01	NS
RPP	0.001	0.05	0.01	NS
$\dot{V}_E$	NS	NS	NS	NS
f	NS	NS	NS	NS
V_T	NS	NS	NS	NS

* Values indicate whether or not hemorrhage had a statistically significant effect on indicated variable. p is less than the numerical value shown. NS = $p > 0.05$. Abbreviations are defined in footnote to Table 1.

At each level of oligemia, left-sided filling pressure was higher with ketamine than with halothane, which in turn was higher than with isoflurane, which in turn was higher than with enflurane. Stroke volume was always lower with enflurane and ketamine (no significant difference between the two) than with isoflurane and halothane (no significant difference between the two). Heart rate was always higher with ketamine than with all inhalation anesthetics, which did not differ among themselves. Therefore, cardiac output at normovolemia and during 10% blood loss was highest with ketamine and lowest with enflurane; there was no difference between isoflurane and halothane. However, as blood loss increased, $\dot{Q}$ decreased to a greater extent with ketamine (0.120 L/min/percentage of blood loss; linear regression, $r^2 = 0.99$) than with the inhalation anesthetics (halothane 0.077, isoflurane 0.071, enflurane 0.058 L/min/percentage of blood loss; $r^2 = 0.98$ to 1.00), so that there was no difference in $\dot{Q}$ after 20% blood loss among ketamine (3.58 ± 0.27 L/min), isoflurane (3.52 ± 0.13 L/min), and halothane (3.10 ± 0.14 L/min); or after 30% blood loss among ketamine (2.48 ± 0.15 L/min), isoflurane (2.83 ± 0.19 L/min), and halothane (2.45 ± 0.19 L/min). Cardiac output with enflurane was less at all levels of oligemia than with any other agent. Compensation for the decrease in $\dot{Q}$ by an increase in SVR occurred during hemorrhage with all agents, but to varying degrees. Although there were no differences in SVR among agents before hemorrhage, after 30% blood loss SVR was greatest with ketamine; SVR was greater with halothane than with enflurane, which was greater than with isoflurane. With all agents, compensation was incomplete, and consequently $\overline{BP}a$ decreased progressively with graded oligemia. At all levels of blood loss, $\overline{BP}a$ was always greater with ketamine than with halothane, which was greater than with isoflurane, which was greater than with enflurane.

During normovolemia and at all stages of graded blood loss, no differences in mean pulmonary arterial pressure or PVR occurred among the anesthetic agents. At each stage of graded hypovolemia, stroke work and minute work were least with enflurane. Rate-pressure product was greater with ketamine at every level of blood loss than with all inhalation anesthetics.

Tissue oxygen extraction at all levels of hypovolemia was least with halothane but did not differ among the other agents. Total body oxygen consumption at normovolemia and at 10% and 20% blood loss was higher with ketamine than with the inhalation anesthetics; at 30% hemorrhage, $\dot{V}_{O_2}$ decreased significantly with ketamine. There was no difference in $\dot{V}_{O_2}$ among the agents after 30% blood loss.

These differences in $\dot{V}_{O_2}$ were reflected in arterial blood lactate concentrations and calculated base excesses. In response to hemorrhage, arterial blood lactate concentration increased only when animals were anesthetized with ketamine; after 30% hemorrhage, blood lactate concentration was higher during ketamine anesthesia than during anesthesia with all other agents. Similarly, base deficit increased with hemorrhage during ketamine anesthesia to a greater extent than with the inhalation anesthetics, so that after 10% blood loss, base deficit was higher with ketamine than with halothane and enflurane. After 20% and 30% loss, base deficit was greater with ketamine than with any of the inhalation anesthetics.

Because of their incomplete nature, data from two additional animals have been omitted; these animals died as a result of ketamine studies. During a ketamine experiment one animal died from progressive, uncontrollable hyperthermia and cardiovascular collapse. The other dog died 36 hours after failing to

TABLE 6

Statistical Comparison of Ketamine (K), Halothane (H), Isoflurane (I), and Enflurane (E) at Normovolemia and at Each Level of Hemorrhage in Five Dogs*

	Normovolemia	Blood Loss (%)		
		10	20	30
$\overline{BP}a$	K>H>I>E			
HR	K>I=E=H			
$\dot{Q}$	K>I=H>E		K I H>E	I=K=H>E
SV	I=H>K=E			
LVSW	K=H>I>E		H=K=I>E	
LVMW	K>H=I>E			K=H=I>E
$\overline{SVR}$	E=K=H=I	K=H=E>I		K>H>E>I
$\overline{PAP}$	NS			
PVR	NS			
$C(a-\bar{v})_{O_2}$	E=K=I>H			
$\dot{V}_{O_2}$	K>I=E=H			K=I=H=E
T_{O_2}	K>H=I>E		K=I=H>E	
$T_{O_2}/\dot{V}_{O_2}$	H>I>E=K	H I E K	H I E K	H=I=E=K
Pa_{O_2}	K E=I H			
Pa_{CO_2}	I>E=H>K			
pHa	K>H>E>I	K>H=E>I	K E H>I	E=K=H>I
BE	E=H=K=I	E>H I K	E>H=I>K	
Hct	NS			
Lactate	NS			
PAPw	K=H>I>E	K>H>I>E		
RPP	K>H=I=E			
$\dot{V}_E$	K>H=E=I			
f	K>I=H=E			
V_T	NS			

* Abbreviations are defined in footnote to Table 1, NS, no significant difference among agents. Agents listed in descending order of magnitude, > indicates all agents to left of symbol are statistically ($p < 0.05$) greater than all agents to right. $\overline{a\ b\ c} > d$ indicates *a*, *b*, and *c* are all greater than *d*; *a* is greater than *c*, but not greater than *b*; nor is *b* greater than *c*. Similarly, $a\ \overline{b\ c\ d}$ indicates that the only statistically significant difference is that *a* is greater than *c* and *d*. $\overline{a\ b} = \overline{c\ d}$ indicates that *a* is statistically greater than *c* and *d*, and *b* is statistically greater than *d*.

recover from a ketamine experiment in which, after 30% hemorrhage, $\dot{Q}$ and $\overline{BP}a$ were lower and base deficit was higher than during the comparable period of the halothane experiment in the same dog. No deaths or complications occurred during or after experiments with any inhalation anesthetic.

Discussion

In general, the influence of anesthetic agents in our dogs was similar to that observed by others in dogs (10, 21-29) and in man (30-39) (Kopriva CJ. Hemodynamic effects of intravenous ketamine in patients with coronary artery disease. Abstracts of Scientific Papers. Annual Meeting of the American Society of Anesthesiologists, October 1974, pp 233-4). No other study has directly compared these four anesthetic agents in the same animals, although Miller et al (40) recently compared halothane, enflurane, and ketamine in normovolemic rats. Differences between the two studies may be a result of differences in species and/or experimental protocol.

In comparing these four anesthetics during normovolemia, only ketamine produced cardiovascular stimulation. Enflurane in equi-MAC concentration produced greater cardiovascular depression than either isoflurane or halothane. All inhalation anesthetics decreased total body oxygen consumption, but only halothane and isoflurane reduced oxygen demand more than oxygen supply.

Comparison among Anesthetic Agents of Physiologic Sequelae of Hemorrhage

The cardiovascular stimulation seen with ketamine during normovolemia persisted during hemorrhage. At all levels of blood loss, left heart filling pressure, heart rate, and mean arterial blood pressure were

always greatest with ketamine. Similarly, in response to graded blood loss, SVR increased most with ketamine. However, despite the stimulation, cardiac output decreased more with blood loss during ketamine anesthesia than during anesthesia with any of the inhalation anesthetics. After 30% blood loss, no statistical difference in $\dot{Q}$ occurred among ketamine, isoflurane, and halothane. As a result, minute work, rate-pressure product, and oxygen consumption during hemorrhage were always highest with ketamine. After 30% blood loss, $\dot{V}_{O_2}$ decreased with ketamine, but did not change with the inhalation anesthetics, suggesting that oxygen demand was not met at this level of blood loss during ketamine anesthesia. This hypothesis is supported by the more pronounced changes in base excess in response to hemorrhage with ketamine and by the increase in blood lactate concentrations seen only with ketamine during blood loss. It is well documented that hemorrhage increases sympathetic activity (41). Short-term benefits of such stimulation are obvious: increased cardiac output and mean arterial blood pressure. It is far from clear that the cardiovascular gain is worth the metabolic price.

Our results are in some ways analogous to those of Theye et al (7), who compared survival times during removal of 0 to 40 ml/kg of blood from ventilated dogs with intact spleens who were anesthetized with cyclopropane, halothane, or isoflurane. Before blood loss, cyclopropane resulted in higher cardiac output and mean arterial blood pressure than either halothane or isoflurane. The authors (7) attributed their results to higher arterial concentrations of epinephrine during cyclopropane anesthesia. Their observations, in part, also may have been a reflection of the direct vasoconstrictive action of cyclopropane (42) and/or its lesser net myocardial effects (43). With hemorrhage, $\dot{Q}$ and $\overline{BP}a$ decreased more with cyclopropane than with either inhalation anesthetic, and arterial epinephrine increased more with cyclopropane than with either inhalation anesthetic. Total body oxygen consumption decreased the most, and arterial lactate concentration increased the most with cyclopropane. Survival time was shorter with cyclopropane than with either isoflurane or halothane. Our results with ketamine are similar to those obtained with cyclopropane (7). By anesthetizing our dogs with each anesthetic agent and following an identical hemorrhage protocol each time, we found that ketamine, like cyclopropane, does not appear to be as useful for maintenance of anesthesia during hemorrhage as agents that are not sympathetic stimulants.

Longnecker and Sturgill (44), using rats that were bled to $\overline{BP}a$ of 40 torr for 1 hour, found a higher survival rate in rats anesthetized with ketamine than in those anesthetized with pentobarbital or halothane. Longnecker and Sturgill speculated that ketamine may have increased survival rate in these animals because a balance between oxygen demand and delivery was maintained. However, they did not measure blood gas tensions, cardiac output, regional blood flow, oxygen consumption, or blood lactate concentration. Our dogs required a higher F_{IO_2} to maintain Pa_{O_2} at 100 torr when anesthetized with the inhalation anesthetics than when anesthetized with ketamine. Because Longnecker and Sturgill's rats breathed room air, it is possible that their animals which were anesthetized with halothane were hypoxic. Although we did not measure regional blood flow or metabolism, our total body data do not support the concept that ketamine maintains a balance between oxygen demand and delivery.

The lack of change in heart rate with hemorrhage that we noted has also been observed previously by others (3-5). Reviewing several hundred of his experiments on dogs, Wiggers (45) noted that heart rate response to hemorrhage was somewhat variable. He found that, in general, when heart rate was initially below 100 beats per minute, it increased in response to hemorrhage; that when it was initially 150 beats per minute or greater, it tended to decrease in response to hemorrhage. Inasmuch as the initial heart rates of our dogs were approximately 120 beats per minute, it is not surprising that heart rate did not change with hemorrhage.

In man, duration of anesthesia alters the cardiovascular actions of halothane (33) and enflurane (30, 31) but not of isoflurane (37, 38). There is no evidence that such recovery occurs in dogs. Each of our studies took several hours, the mean time between induction of anesthesia and measurements made after 30% blood loss being 282 minutes. The measurements taken in normovolemic animals during the early part of the anesthetic procedure and those taken late in the anesthetic procedure after return of the shed blood did not differ significantly. Also, during several hours of ketamine anesthesia without hemorrhage, measured and calculated variables did not change. These two facts indicate that no functional mechanism altered cardiovascular function with time during anesthesia.

As our animals breathed spontaneously, Pa_{CO_2} varied among anesthetic agents (Tables 5 and 6). The dogs were mildly hypocarbic with ketamine, hypercarbic with isoflurane, and nearly normocarbic with

halothane and enflurane. Cardiovascular stimulation caused by carbon dioxide is blunted by halothane (35, 36), isoflurane (37), cyclopropane (46), and fluroxene (47). Cardiovascular depression seen with enflurane during controlled ventilation (31) is eliminated when P_{aCO_2} is allowed to increase with spontaneous ventilation (30). However, after several hours of enflurane anesthesia with spontaneous ventilation in volunteers, P_{aCO_2} returned to near normal values, but cardiovascular depression did not become evident. Thus, at the time we performed our measurements, it appears that the relationship of cardiovascular stimulation by CO_2 during enflurane anesthesia is altered. It is possible that differences in P_{CO_2} influenced our results. There are no data regarding the interaction of hemorrhage, anesthetic anesthetics, and carbon dioxide; however, the relatively mild hypocapnia seen with ketamine (e.g., P_{CO_2} 33 torr at 30% blood loss) is not likely to have resulted in major hemodynamic changes.

Clinical Implications

Our data suggest that ketamine may be less desirable than halothane or isoflurane for maintenance of anesthesia during moderate hypovolemia. However, it may be inappropriate to translate these studies in animals directly to man. Differences and similarities in the cardiovascular effects of anesthetic agents between man and dog during normovolemia may not be the same during hypovolemia. Finally, our experiments did not study the effects of anesthetics used for induction of anesthesia in the presence of preexisting hypovolemia, and consequently we can make no comment in this regard. The considerations and consequences of producing acute sympathetic stimulation, as during induction of anesthesia, may not be similar to those during the more prolonged maintenance of anesthesia.

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Specificity of Postoperative Perfusion Lung Scan Defects

Ventilation and perfusion lung scans were performed before and after surgery in 169 patients and classified blindly according to preset criteria. Patients admitted to the hospital for major elective surgical procedures were selected for the study provided they gave informed consent and provided perfusion and ventilation lung scanning facilities were available in the department of nuclear medicine. Whenever possible, patients clinically judged to be at high risk of pulmonary embolism were selected over patients at low risk. No specific prophylaxis against venous thrombosis was used, but early ambulation was encouraged. Perfusion lung scan abnormalities were present in 25 (15%) of the preoperative scans and 42 (25%) of the postoperative scans; 16 (38%) of the abnormal postoperative scans were ide[illegible]h the preoperative scans. Perfusion defects indicating a "high probability" of pulmonary e[illegible] (lobar or segmental defects) were present in five preoperative scans and 10 postoperative scans; the 10 postoperative scans were classified as showing "definite" (five scans), "possible" (one scan), or "no" (four scans) pulmonary embolism on the basis of the preoperative scan and the ventilation scan; none of the 10 patients had clinical evidence of pulmonary embolism. Venous thrombosis was present in 12 patients, including four of the patients whose lung scans showed definite pulmonary embolism. Thus, postoperative perfusion lung scan defects even when large, are potentially misleading. (*Walker I, Aukland P, Hirsh J, et al: The low specificity of postoperative perfusion lung scan defects. Can Med Assoc J 1981;124:153-8*)

ANESTHESIA FOR MAJOR TRAUMA

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ANESTHESIA FOR MAJOR TRAUMA

This chapter will emphasize the anesthesiologist's role in the management of patients with major trauma, particularly those features which relate to airway management and fluid resuscitation. Problems peculiar to some of the more common major injuries will also be outlined.

INITIAL EVALUATION AND MANAGEMENT

Airway and Gas Exchange

On arrival in the emergency room, all seriously traumatized patients should receive oxygen, since many physiological sequelae of trauma result in arterial hypoxemia while breathing air. The chest should be auscultated bilaterally and, if there is any question of a possible chest injury, radiographs should be obtained immediately. Hemo or pneumothoraces should be relieved by placement of large bore chest tubes. Patients in whom systemic blood pressure is unobtainable require immediate intubation of the trachea and ventilation with 100% oxygen as part of the initial emergency room resuscitation sequence (rapid intravenous fluid administration and, if necessary, thoracotomy and aortic cross-clamping). Fixed dilated pupils, in and of themselves, are not an accurate indication of irreversible CNS damage and do not contraindicate aggressive management at this time[1,4,5]. If an esophageal obturator has been previously inserted, it should not be removed until the airway is protected with an endotracheal tube, because of the likelihood of regurgitation of gastric contents and the possibility of subsequent aspiration. Patients who are markedly hypotensive despite rapid intravenous infusion

also require early intubation to support gas exchange and protect the airway, since cerebral ischemia commonly causes muscular flaccidity and regurgitation of gastric contents. The decision as to when to intubate a hypotensive awake patient in the emergency room is difficut; these patients are usually candidates for immediate surgery because of continuing gross hemorrhage. If anesthesia is necessary for intubation of the trachea, we use a ketamine-succinylcholine sequence described later in this chapter.

Facial fractures and upper airway injuries. Airway assessment is the main early requirement in this group of patients. Massive facial injuries may result in nasal obstruction, oropharyngeal edema, and hematomata of such magnitude that immediate tracheotomy or cricothyroidotomy is necessary in the emergency room. In all other cases the rate of progress of any swelling in the upper airway must be evaluated. The principle is to ensure the maintenance of a patent airway and to avoid limitation of available techniques by "sudden" airway obstruction. In patients with major fractures of the mandible and maxilla (LeForte III), but in whom massive edema has yet to occur, oral intubation is preferred and is usually easily accomplished, should this be required. In the most obtunded, the trachea may be intubated without anesthesia. If this situation is misjudged, vomiting may occur and strong suction must be immediately available. Blind nasal intubation may be hazardous because of potential false passages into nasal sinuses and the cranial vault, and the possibility of dislodging loose bone and tissue. It is unusual for an alert cooperative patient with facial injuries to require intubation in the emergency department. However, if this is necessary, the alternatives for direct

laryngoscopy and intubation are a) topical anesthesia, spraying anesthetic and advancing the laryngoscope in a series of stages, or b) general anesthesia with preoxygenation, cricoid pressure, thiopental or ketamine and succinylcholine. Fractures of the mandible alone usually do not cause airway difficulties, when the larynx is normal (see below).

Injuries of the larynx may cause rapid respiratory obstruction and require immediate tracheotomy. In less urgent situations, and when assessing the possibility of such an injury, a history of trauma to the head and neck, stridor, hoarseness, and crepitus in the neck are all suggestive. The most frequent cause of a fractured larynx is direct force from a deceleration injury. A fracture in the region of C6 or C7 is a common association. Three useful evaluative tests for laryngeal fracture are a) asking the patient to make a high-pitched "EE" sound which requires mobile cricoarytenoid joints, normal tense cords and functioning intrinsic laryngeal neuromuscular mechanisms; b) indirect laryngoscopy; c) radiography of the larynx, especially CAT scan. If uncertainty exists, fiberoptic laryngoscopy may be performed under topical anesthesia. If this type of injury is suspected, all possible information should be accumulated prior to induction of general anesthesia, since laryngeal obstruction may occur during attempted tracheal intubation. The latter may cause mucosal stripping, bleeding, or displacement of fractured cartilage into the airway lumen.

When a fractured larynx is present, laryngofissure and repair of mucosal lacerations and cartilage fractures are frequently carried out. Classically, a tracheotomy under local anesthesia is performed first. Alternatively, there are recent reports of successful tracheal intubation through the glottis[2]. This should be attempted only in the presence of the most benign preoperative findings and when laryngeal visualization is excellent. If a tracheotomy is

necessary in an uncooperative child, it may be accomplished following a small dose of ketamine as a supplement to local anesthesia.

IN ALL CASES OF POSSIBLE AIRWAY COMPROMISE, WHEN IT IS UNCERTAIN WHETHER THE PROPOSED ANESTHESIA MANUEVERS WILL BE SUCCESSFUL i.e. AIRWAY OBSTRUCTION COULD OCCUR, THE PROCEDURES SHOULD BE CARRIED OUT IN AN OPERATING ROOM WITH EQUIPMENT AND PERSONNEL READY FOR IMMEDIATE TRACHEOTOMY.

Head injuries. A high percentage of unconscious patients with recent head injuries require intubation for one or more of three indications: 1) to overcome airway obstruction, 2) to prevent aspiration of secretions and 3) to ensure hyperventilation to minimize intracranial pressure. If it is decided not to intubate a patient who has a fresh head injury, he must be observed closely; personnel able to intubate him must be readily available. Sudden rapid deterioration occurs quite commonly within the first few hours and therefore a single evaluation is not sufficient. When possible, cervical films are obtained prior to intubation although, in our experience, neck fractures are quite rare in patients who require intubation for head injury. If an unstable neck is suspected, a cervical collar is placed and oral intubation may be attempted using a "hockey-stick" bend created at the tip of the endotracheal tube by means of a stylet. If oral intubation appears technically straight forward, we do not hesitate to use muscle relaxants with application of cricoid pressure, following a period of preoxygenation. The surgeon should hold the head during this intubation and warn of any impending excessive extension. The alternatives are blind nasal intubation, which may be easy in

the hyperventilating patient or, if time permits, intubation over a fiberoptic bronchoscope. If all else fails, tracheotomy may be necessary.

Barbiturates, other hypnotics or muscle relaxants may be required to control restlessness, either to permit CAT scanning or angiography or to prevent an increase in intracranial pressure due to straining secondary to the irritation of an endotracheal tube. The ability to conduct neurological assessment is thereby lessened but this should not be of concern. Either a surgical decompression is indicated by the radiological findings or, if not, an intracranial pressure line may be inserted to permit accurate ongoing evaluation.

Fluid Resuscitation

In any patient in whom a major injury is suspected, at least two large bore intravenous cannulae should be inserted, one of which should be located centrally (superior vena cava or right atrium). One should not depend upon lower extremity lines for infusion in those patients where disruption of iliac veins or inferior vena cava is a possibility (pelvic, abdominal or chest trauma). A catheter should be placed in the bladder in all patients. Those who have decreased skin perfusion with resultant pallor and coolness, narrow pulse pressure, tachycardia, and orthostatic hypotension, are likely to have lost in excess of 20-25% of their blood volume. Cardiac output will have decreased in approximate proportion to blood loss. Deterioration of mental status indicates more severe loss of blood volume, usually in excess of 40%. Fluid resuscitation should be started; it is useful to sequentially number each new bag of fluid. Blood volume should be restored to at least a level at which a CVP of several

mmHg is obtained. If crystalloid is used for this purpose, 3 or more liters may be required if the above signs are present. If a pneumatic suit ("G" or "MAST" suit) has been inflated around the victim's abdomen and lower limbs, a variable but potentially large amount of intravascular volume may have been shifted centrally[3,21]. The measured CVP will then not be an accurate reflection of total intravascular volume. The suit should be deflated one compartment at a time, with careful observation of hemodynamic status, when volume replacement has started and immediate surgery can be performed if necessary.

Premedication Agents

These should not be used routinely. Extreme caution is necessary in hypovolemic patients, and agents without effective antidotes should be avoided. Although narcotics are effective in relieving pain and anxiety, they dilate peripheral blood vessels and may produce further hypotension with resultant cerebral ischemia adding to the sedative effect of the narcotic, causing regurgitation of gastric contents and aspiration. Cimetidine, 300 mgm intramuscularly, is sometimes advocated as a means of decreasing gastric acidity in emergency surgery patients. This is not universal practice and we do not do this routinely.

OPERATING ROOM MANAGEMENT

Preparation of Equipment

To provide anesthetic care for major trauma at a moment's notice a completely ready operating room should be available at all times. The anesthesiologist should have the following recently checked-out equipment in place: 1) anesthesia machine; 2) volume controlled ventilator, with appropriate values preset;

3) suction; 4) laryngoscope with spare blades, and endotracheal tubes with stylets; 5) appropriate drugs (pancuronium, succinylcholine, ketamine) drawn into labelled syringes; 6) two intravenous infusion sets with pumps and blood warmers, prefilled wth crystalloid solution; 7) material required for arterial line placement; 8) warming blanket and/or a device to provide heated humidified inspired gases; 9) defibrillator with internal and external paddles; 10) calibrated equipment to monitor: a) electrocardiograph, b) arterial blood pressure, c) central venous pressure, d) neuromuscular blockade, e) temperature.

Choice of Anesthetic (Regional or General)

In choosing between regional and general anesthesia, we prefer the latter for the more major injuries, particularly in the presence of an unstable cardiovascular status or injuries of the abdomen or thorax. Spinal anesthesia does not permit control of ventilation and the resultant sympathetic block prevents an important homeostatic response to hypovolemia. In patients with abdominal injuries, the extent of the necessary exploration and procedures is usually uncertain preoperatively, therefore precluding limited block levels. On the other hand, infiltration anesthesia or regional blocks can be extremely useful for the management of the more minor peripheral injuries, provided attention is paid to the maximum safe dose of the agent selected relative to the patient's body size and physical status.

Induction and Maintenance of General Anesthesia

During induction of anesthesia, aspiration of gastric contents into the lungs may follow passive regurgitation or active vomiting. The latter may be avoided by using a rapid intravenous induction sequence. When diaphragmatic relaxation occurs secondary to

cerebral ischemia, heavy sedation or anesthesia, passive regurgitation may occur, due to the pressure difference between abdomen and thorax. Several hours delay in scheduling surgery may decrease the probability of food remaining in the stomach, but this is never totally reliable and may be contraindicated by the urgency of the injury. A low gastric acidity and/or an empty stomach cannot be assumed for extended periods following trauma. Therefore, the following steps should be taken: 1) in all cases of intestinal obstruction, ileus, or gastroduodenal perforation or bleeding, a nasogastric sump tube should be placed and the stomach aspirated immediately prior to induction (although this does not ensure an empty stomach); 2) the probable ease of laryngoscopy and oral intubation should be assessed; 3) with powerful suction available, anesthesia should be induced using a small dose of non-depolarizing muscle relaxant (this may minimize an increase of intragastric pressure when succinylcholine is subsequently administered[49]), preoxygenation for at least 3 minutes of quiet breathing or 4 or 5 maximum inspirations, then antero-posterior pressure applied over the cricoid cartilage (compressing the upper esophagus[51]), and a rapidly acting intravenous hypnotic and muscle relaxant (usually succinylcholine) administered intravenously. Laryngoscopy, tracheal intubation, cuff inflation and tube location checks are carried out before removing cricoid pressure. If laryngoscopy and intubation are expected to be difficult, other options, in order of preference, are intubation (nasally or orally) under topical anesthesia - if necessary with a fiberoptic bronchoscope, or a tracheotomy under local anesthesia. In many acute injuries of the jaw and neck, in which the state of the pharynx is in doubt, we prefer

oral intubation under vision as a first step. Then, if nasal intubation is required, a nasal tube may be advanced under direct vision with the larynx in full view and the airway protected. This permits full evaluation of the injury prior to nasal intubation.

Whenever possible, hypovolemia should be corrected prior to transport to the operating room and induction of anesthesia. If correction is not possible because of the nature and extent of the injuries (i.e. the rate of hemorrhage exceeds the ability to restore intravascular volume) it may be necessary to induce "anesthesia" in the hypovolemic patient. If the patient is unconscious or severely obtunded, intubation of the trachea should be accomplished without drugs or with neuromuscular blocking agents alone. If the patient is conscious despite being uncorrectably hypovolemic, other techniques are required. For many years it was common practice to use an ultra-rapidly acting thiobarbiturate (e.g. thiopental) for inducing anesthesia in this circumstance, frequently resulting in acute decompensation (including death) in an already severely hypotensive patient[16,24]. These clinical observations may be attributed to the myocardial depression and decreased peripheral venous tone caused by these agents[15,19]. Ketamine is a rapidly acting intravenous agent that, in normovolemic, healthy patients and laboratory animals, results in increased heart rate, systemic vascular resistance, blood pressure, and cardiac output[50,64]. These are indirect effects caused by increased central sympathetic outflow and baroreceptor blockade and decreased vagal tone[14,63]. Very small doses of ketamine (0.35 - 0.7 mg/kg IV) are useful for inducing "anesthesia" in hypovolemic, hypotensive conscious

patients. If a dose greater than that dictated by the clinical situation is used, the indirect stimulatory responses are not elicited, and ketamine's direct action of myocardial depression[7] may result in cardiovascular decompensation. Once intubated, the patient should be mechanically ventilated to free the anesthesiologist's hands. Evidence is lacking that either respiratory acidosis or alkalosis is beneficial during massive hypovolemia. We therefore attempt to maintain normocarbia, which has the added advantage of not confusing interpretation of acid-base status.

Following induction, only oxygen and neuromuscular blocking agents are administered until the hemodynamic situation is stabilized and systemic blood pressure rises to a mean of at least 50 torr. At that point cerebral perfusion should be adequate and it is then appropriate to consider the administration of other agents. The goal is to provide analgesia or amnesia with minimal cardiovascular disturbance. Since the clinical situation is still in great flux and conditions may deteriorate, in principle, agents which are easily removed or whose actions are readily terminated should be used. Cyclopropane and ether are contraindicated because of the risk of explosion in a setting of multiplicity of personnel and electrical equipment. Furthermore cyclopropane decreases survival time in shocked dogs[61]. Halothane, enflurane or isoflurane may be cautiously added in very small concentrations (e.g. halothane 0.1%) to the background of 100% oxygen, and its cardiovascular effects observed. All the inhalation agents are direct myocardial depressants[8,10,57] and may result in significantly decreased myocardial performance and hypotension,

if added too rapidly or in too great a concentration. Recent data suggests that isoflurane and halothane may be superior in these circumstances when compared with enflurane[69]. The anesthetist must pay extremely close attention to the variable clinical situation and be prepared to cease administration of all inhalation agents should hypotension ensue. Although nitrous oxide is a superior analgesic, it is frequently depressant in the hypotensive hypovolemic patient. Since it must be used in relatively high concentrations, this adds to the potential for hypoxia because of decreased inspired oxygen concentration. Furthermore, nitrous oxide will increase the volume of any previously unrelieved pneumothorax and will increase bowel distention. Although narcotics have been used in such circumstances, two objections may be raised. Once given, they cannot be removed as can the inhalation agents. Second, the use of naloxone to reverse narcotic action may be only partially successful because of hypoperfusion at the site(s) of action and because of shorter duration of action of the antagonist than the agonist. Recent evidence that administration of naloxone is of benefit in non-narcotized shocked animals suggests that endorphins and, thus, perhaps narcotics are detrimental in such circumstances[70]. We have not observed awareness of pain in any patient questioned postoperatively following this conservative approach to the use of CNS depressants.

In selecting a muscle relaxant for continued use during the procedure, d-tubocurarine is avoided because of its propensity to release histamine, resulting in further hypotension. Pancuronium is preferred to gallamine because of its greater vagolytic properties[57] and its lesser obligatory dependance

on renal excretion[17]. Metacurine and NC45 (not yet clinically available) have the least cardicvascular actions of non-depolarizing muscle relaxants[1].

Hemodynamic Management

After securing the airway and establishing ventilation, hemodynamics remain the primary issue. Because of the rapidity and intensity of physiological response to hemorrhage (increased sympathetic system activity, increased renin-angiotension system activity, increased vasopressin, peripheral circulatory effects, acidic metabolites, direct hypoxic effects, fluid shifts) and the multiplicity of therapeutic manuevers in the acute situation, the hemodynamic status of the patient will change rapidly. Accordingly, accurate beat-to-beat blood pressure monitoring is an important aspect of the acute management. For this reason and to allow repeated, rapid sampling of arterial blood for measurement of PO_2, PCO_2 and pH, an indwelling arterial cannula should be placed as early in the operating room sequence as feasible, if necessary by surgical cut-down, and connected to a pressure transducer for continuous measurement of blood pressure. The arterial line should be placed in the upper extremity because it may be necessary to cross-clamp the thoracic aorta. A central venous (superior vena cava or right atrial) cannula should be placed, time permitting, while the patient is in the ER, or soon after arrival in the OR. In the operating room, introduction through an internal jugular vein is favored over the approach from an antecubital or subclavian vein, both because of the ease and rapidity of insertion through the former and the accessibility of this route while surgery proceeds. To permit continuous accurate assessment of central venous pressure,

and for rapid verification of position, the cannula should be connected to a pressure transducer. The preponderance of major trauma victims are young and without heart disease, thus central venous pressure will usually be an adequate reflection of left-sided filling pressure[35]. Placement of a pulmonary arterial line in the early care of the massively traumatized patient is neither necessary nor advisable; time is better spent tending to higher priority issues. If there is a need for intra-operative left-sided filling pressure (e.g. failing post-ischemic ventricle, high suspicion of pre-existing significant myocardial disease or direct ventricular injury) a left atrial catheter may be inserted directly if thoracotomy has been performed. Direct observation of the degree of filling of the heart is also useful in the evaluation of the patient's volume status. The early stages of resuscitation of the massively bleeding patient require continuous communication between the surgeons and the anesthetists, as to the nature and extent of the injuries and the hemodynamic indices. If it is necessary to cross-clamp the aorta to provide adequate blood flow to the brain and heart in the face of massive hypovolemia, subsequent removal of the clamp may cause hypotension from circulating volume filling a previously empty, acidotic vascular tree. Consequently, re-perfusion should be established gradually as hemodynamics permit, with addition of volume or base or both, as required (see below).

Intra-operative fluid resuscitation. The amount of fluid volume to administer is guided by the systemic blood pressure and the cardiac filling pressure. Fluids are administered as rapidly as possible until the CVP is in the normal range for an anesthetized patient (e.g. 10-12 cmH_2O), and/or the systemic blood pressu

is in the normal range (see below for a discussion of hypotension in the face of apparently adequate volume replacement). Much research and discussion has surrounded the issue of which fluid to administer. The clinician may currently choose from 1) whole blood, 2) packed cells, 3) salt solutions (crystalloid), 4) protein containing fluids (colloid) or 5) other osmotically active agents (e.g. dextran). Whole blood is the fluid of choice despite some deficiencies of banked blood (see below). Whole blood offers the advantages of the ability to transport and on and off-load oxygen and carbon dioxide, contains most clotting factors in adequate supply, and is a good buffer at physiological pH. The disadvantages of banked blood include a) low storage temperature (4°C) with high thermal capacity; b) decreased clotting factors V, VIII, and possibly XI; c) lack of functional platelets after 24 hours of storage; d) low pH; e) high potassium concentration; f) decreased red cell survival; g) presence of red cell membrane antigens requiring typing and cross-matching the patient's blood with the blood to be transfused (although the U.S. Army had highly favorable experience in Viet Nam using unmatched low anti-A, anti-B titer group O[7,9,10] and the need for cross-match has been questioned recently[11]); h) presence of citrate; i) risk of transmission of hepatitis; and j) decreased red cell 2,3-DPG concentration resulting in high hemoglobin affinity for oxygen. Blood banks are increasingly fractionating whole blood into its component parts, separating plasma from red cells. Consequently, we must often rely on packed red cells ordinarily spun to a hematocrit of approximately 70%. To decrease viscosity and thus ease

administration, packed cells should be reconstituted to an approximately normal hematocrit prior to transfusion. 0.9% NaCl is the only fluid recommended by the American Association of Blood Banks for use for this purpose[40]. Because packed cells contain little plasma, some of the advantages of whole blood are diminished. Oxygen transport is not affected, however, and CO_2 transport capability is only somewhat decreased as is buffering capacity and, of course, all clotting factors.

Despite considerable laboratory and clinical investigation, there is no firm evidence that the use of microfilters for blood administration is beneficial[60]. The resistance of these greatly impedes rapid blood administration, and we therefore do not recommend their use in this setting.

Note that when extremely rapid infusion of viscous fluids is required there is a considerable difference in resistance to flow between various types of infusion equipment and blood warmers. Stopcocks offer high resistance and, therefore, should not be used.

Inevitably, until the trauma victim's blood is typed, fluids other than blood must be administered. Current evidence indicates that, in this regard, colloid is of no advantage over crystalloid[14,25,33,34,45,59,68] and in fact, may be detrimental[28,35]. Given the expense of the former and the availability and ease of administration of the latter there seems to be little, if any, reason to administer colloid in the acute resuscitative period. Resuscitative fluids undergoing research and development include fluorocarbons and stromal free hemoglobin either in solution or encased in layers of lipid. Oxygen content of fluorocarbons is proportional to the partial pressure of oxygen in the fluid, reaching acceptable oxygen content only at very high PO_2. Furthermore,

fluorocarbons are extremely expensive, with extraordinarily long half-lives. Recently it has been possible to prepare hemoglobin with very little, if any, stromal elements, thus, eliminating renal toxicity[46], and offering the advantage of high oxygen content at normal PO_2. Furthermore, hemoglobin so prepared can be stored in its crystalline form at room temperature for prolonged periods of time. Since no red cell membranes and antigens are present, standard blood typing is unnecessary. Current research is focused on solving the problems of short intravascular half-life (2-4 hours) as a result of renal excretion, and low P_{50} (approximately 14 torr) of this solution of hemoglobin monomers. Nevertheless stromal free hemoglobin has been shown to be superior to albumin in supporting myocardial function[41]. Should the half-life and low P_{50} problems be resolved, stromal free hemoglobin may find its place in the earliest phases of resuscitation of the massively bleeding patient.

Persistant hypotension despite apparently adequate fluid administration. This situation is observed at some stage in the operating room management of many patients who have sustained extremely major injuries. The first checks should be of the accuracy of the monitoring system.

Transducers and monometers must be appropriately positioned and it is useful to have placed a blood pressure cuff on the limb which has been cannulated for the arterial pressure. The occlusion pressure can then be used as a cross-check. Possible causes of the continuing hypotension must then be reviewed. These include undetected hemorrhage (e.g. unexplored body cavities, fractured limbs, lacerated scalp, full thoracostomy containers

concealed by drapes); hemo or pneumothorax or pericardial tamponade; acidosis; hypothermia; ventilation or anesthesia administration error; hypocalcemia may be present in extreme cases of hypoperfusion, hypothermia and massive transfusion.

If correction of acidosis (see below) is ineffective in restoring systemic pressure, we empirically administer calcium chloride 1 gm intravenously since ionized calcium measurements are not readily available. Calcium and other pressors have diminished effectiveness during acidosis.

Myocardial failure in a previously healthy young trauma victim is not common without direct myocardial injury or prolonged myocardial hypoxia. However, if all other possible causes have been excluded or treated, additional fluids may be administered until the CVP is 20-25 torr. If arterial pressure does not respond, pressor agents (dopamine or dobutamine 3-12 mcg/kg/min IV, initially) may be infused. An unusual cause of myocardial failure following perforating chest injuries is coronary air embolism[52] which may be diagnosed by direct observation of the coronary arteries. The question of the existance of a "myocardial depressant factor (MDF)", in shock is controversial[4,10,32,67]. In addition to hemorrhage metabolic acidosis and hypothermia are the two most common secondary aggravating factors in the massively bleeding trauma patient.

Acid-Base Balance

Poor tissue perfusion results in lactic acid accumulation from decreased availability of oxygen at the end of the electron transport chain, and decreased hepatic uptake of lactate during severe reductions of hepatic blood flow or during severe hypoxia[7,27]. It is not clinically convenient to measure

lactic acid. However, its appearance in the blood will result in a nearly linear increase in base deficit. Base deficit may be rapidly computed from measured arterial PCO_2 and pH[52,53,55]. Arterial blood gases and pH should be measured as soon as possible. The primary treatment of acidosis secondary to hypovolemia is obviously volume replacement. If volume is restored and perfusion pressure is satisfactory, the acidosis will be corrected as the liver takes up lactate and the tissues cease lactate production. Thus, treatment of acidosis per se will not be required. However, if hypotension persists, this may be partially due to acidosis. Ideally, the magnitude of this acidosis should be measured. However, if data is not yet available, it is safe to administer $NaHCO_3$ as a therapeutic test. It is unusual to observe clinically important cardiovascular effects of metabolic acidosis at base deficits less than 10 mEq/L and, in this setting, acidosis of considerably greater magnitude is common. Whole body base deficit is usually calculated from the formula 0.3 BE (mEq/L) x body weight (kg). Thus, 200 or more mEq of $NaHCO_3$ may be required. Since the cardiovascular status is usually unstable when $NaHCO_3$ administraton is indicated, a calculated dose will not provide exact correction. Repeated evaluation is necessary. Based on recent evidence that, over a wide temperature range, vertebrate plasma pH is closely related to the pH of water and ionization of imidazole[47], PCO_2 and pH should be measured at 37°C and not corrected to the patient's temperature. In any event, over the clinical range, computation of base excess is very nearly independent of temperature.

It is not clear whether measured PO_2 should be corrected to the patient's temperature or reported at 37°C. However

temperature correction is necessary for computation of alveolar-arterial oxygen tension difference ($AaDO_2$). Furthermore, in the hypothermic patient, if temperature correction results in error it is on the side of patient safety.

Hypothermia

Poor perfusion, opening of major body cavities, and administration of fluids of temperature less than body temperature, inevitably result in hypothermia. Hypothermia presents multiple dangers. Myocardial function decreases with temperature. In the clinical setting of decreased myocardial pre-load and prolonged poor myocardial perfusion, myocardial hypothermia is poorly tolerated. As myocardial temperature falls to approximately 30°C, arrhythmias become common, with refractory ventricular fibrillation occurring within a further decrease of 1-3 centigrade degrees. Hypothermia adds to the coagulation defects (see below) by causing sequestration of platelets[66]. This phenomenon is reversible with rewarming. Additional problems of hypothermia include alteration of drug action and half-life, and confusion of interpretation of blood gas, pH and acid-base data.

Temperature should be measured continuously by a thermistor or thermocouple placed in the esophagus, just behind the heart, or by use of the thermistor of a thermodilution pulmonary artery catheter, if one has been inserted. These sites are preferred because blood and myocardial temperature are of prime concern, and as blood and myocardial temperature change, temperature will change more slowly at other sites (e.g. rectum)[67].

In the massively bleeding trauma patient it is possible to prevent severe hypothermia, although not possible to maintain

normothermic conditions. All intravenous fluids should be warmed during administration. Commercially available devices can effectively warm blood while producing minimal resistance, thus allowing for high flow rates[48,49]. A plugged-in connected warming blanket should always be in place on the operating table. The device should be set and switched on at 40°C at first notice of a patient's likely transport to the operating room, since these devices require 10 to 20 minutes to reach operating temperature. These blankets, although useful, are of less than optimal value because of poor peripheral circulation during massive hypovolemia. Accordingly, heated inspired humidity may be of value in preventing serious hypothermia since nearly all the right heart output will be exposed as a thin layer to the inspired heat in the pulmonary circulation. If the above measures fail, warm crystalloid solution should be placed in the chest or abdominal cavities.

Coagulation

A bleeding diathesis following massive blood loss and replacement is not uncommon. Causes are 1) lesions of banked blood; 2) hypothermia; 3) consumption coagulopathy; 4) platelet dysfunction. Coagulation factors V, VIII and possibly XI have storage half-lives of approximately one week. Fortunately, only 5 to 30% of the normally present quantities of these factors are necessary for surgical hemostatis. Furthermore, the liver can rapidly produce large quantities of factor VIII, once circulation has been restored[50]. Platelet function is severely impaired within minutes of storage at 4°C, with survival limited to less than 48 hours[31]. Many blood banks remove platelets from blood after its collection. Thus, nearly all blood transfused

is free of functional platelets, creating a dilutional thrombocytopenia[38]. Furthermore, hypothermia causes platelet sequestration[66]. Fresh frozen plasma contains all coagulation factors except platelets. The role of fresh frozen plasma or fresh (less than 24 hours old) whole blood is controversial[12,43,44,54,65].

The coagulopathy of massive transfusion occurs commonly when between one and two times the estimated blood volume has been administered. Ten units of platelets should be administered, if further significant transfusion is anticipated and/or generalized bleeding is apparent. Most hospital blood banks do not stock platelets, thus they may need to be ordered well in advance. Additional units of platelets will be required if hemorrhage is not controlled. Although this is controversial, we also administer two units of fresh frozen plasma after ten units of blood or packed cells and one additional unit for each further 5 units of transfused blood.

Development of a consumptive coagulopathy (possibly resulting from release of tissue thromboplastin) will further deplete the diluted platelets and already decreased clotting factors.

The most convenient method for determining the etiology of a bleeding disorder, in the major trauma victim, is to observe the coagulation time. If, in a glass tube, a good clot does not form, or does so only after a prolonged period of time, decreased clotting factors are implicated. If the clot forms but does not retract, thrombocytopenia is the likely cause. If the clot lyses, fibrinolysis is likely.

Calcium is complexed by citrate in banked blood, but its clinical importance as a cause of the bleeding diathesis[37] of

massive transfusion and of decreased myocardial function[11,26,28] is controversial. We do not administer calcium routinely as prophylaxis against coagulation defects.

SPECIAL TRAUMA PROBLEMS

Thoracic Injuries

Three problems may require special actions by the anesthesiologist.

Pulmonary injuries. Systemic air embolism due to pressure in the alveoli exceeding pressures in adjoining perforated pulmonary vessels is not uncommon[6,7]. Occasionally, massive bronchial air leak may prevent effective mechanical ventilation. Placement of a double-lumen endotracheal tube provides maximal control of this problem, and prevents hemorrhage into the dependent lung during lateral thoracotomy. If this technique is not possible, a long endotracheal tube capable of being advanced into a main bronchus should be used. Inhaled agents should include only oxygen and anesthetic vapor until measurements of pulmonary oxygen exchange are obtained.

Aortic injuries. Prolonged supra-renal clamping of the aorta may cause renal and spinal cord ischemia. The higher the clamp, the greater the likelihood of resultant left ventricular failure from the great increase in afterload. If control below the aortic injury is feasible, a shunt may be placed during the period of clamp-off. Restoration of volume will then prevent the above problems. However, if distal control is not feasible and a shunt is not placed, an agent such as sodium nitroprusside may be required to permit volume loading while the aortic clamp is in place. Arterial pressure monitoring should be from the right arm if the injury may be to the arch of the aorta. If time

permits, left ventricular filling pressure should be monitored.

Cardiac injuries and tamponade. Rapid surgical correction is essential. "Anesthesia" is induced with a small dose of ketamine (0.35 to 0.7 mg/kg) which usually maintains cardiac function, rather than sodium thiopental which depresses venous return and myocardial contractility. Although the maintenance of a high cardiac filling pressure is theoretically important and intravenous fluid should be given to achieve it, this is only a short-term, temporarizing measure.

Spinal Injuries

The approach to securing an airway has been discussed above. Although succinylcholine is contraindicated several days after a denervation injury, there is no evidence of muscle membrane instability in the first few hours. Thus, if otherwise indicated, succinylcholine may be used. Patients in halo traction, requiring anesthesia for other injuries, are intubated nasally under topical anesthesia, if necessary using a fiberoptic bronchoscope. Acute spinal cord injuries, particularly in the cervical or high thoracic regions, result in a "spinal shock" syndrome. Large volumes of intravenous fluid may be required to maintain adequate cardiac filling pressure and systemic pressure. Central venous pressure should be monitored and α-adrenergic agents may be used to compensate for the sympathetic denervation, provided cardiac filling pressures and urine output are maintained.

Head Injuries

Intracranial pressure is decreased as much as possible by administration of mannitol or furosemide, induction of hypocarbia ($PaCO_2$ < 30) and maintenance of a low venous pressure. A mechanical ventilator wave-form with rapid inspiratory flow rates may assist in minimizing inthrathoracic pressure. To

minimize autonomic response to intubation and incision, barbiturates and narcotics, because of their less unfavorable effects on intracranial pressure, are probably preferrable to the anesthetic vapors. However, there is no strong evidence to support large dose barbiturate therapy for brain protection in this setting.

Intraoperative complications. Marked hypotension immediately following intracranial decompression is common. This should be managed with fluids and, if necessary, the judicious use of a pressor such as ephedrine. We routinely establish arterial and central venous pressure monitoring as soon after induction as possible. A coagulopathy is occasionally seen. The etiology of this DIC-like picture is not clear but fresh blood and/or fresh frozen plasma are the therapy of choice. Neurogenic pulmonary edema may be seen rarely and facilities must be available for intraoperative application of PEEP.

The Open Globe

Facial injuries may include trauma to the globe of the eye. Loss of vitreous humor, iris, and lens may result in permanent blindness and require evisceration. To minimize this possibility, every effort is made to avoid raising intraocular pressure. The factors which control intraocular pressure are similar to those affecting intracranial pressure. Induction of anesthesia must be smooth and there must be no "squeeze" of eye muscles or straining during surgery. The fasiculations which accompany succinylcholine administration cause a transient increase in intraocular pressure, but its importance or the effectiveness of a previously administered non-depolarizing agent in the open eye are uncertain. Our

preference includes the use of "precurarization", a large dose of thiopental, and succinylcholine; or, where a large dose of thiopental would be hazardous, substituting a large dose of pancuronium (0.15 mg/kg) for the succinylcholine. Either way, the profound myoneural block is maintained, and monitored with a nerve stimulator. The ventilator is adjusted to maintain hypocarbia.

THE IMMEDIATE POSTOPERATIVE PERIOD

At the end of surgery, for all but the most massive trauma, when hypovolemia has been corrected and the hemodynamic status is stable, the temperature is greater than 34°C, and pulmonary gas exchange is satisfactory, it is usually appropriate to extubate the patient and to administer oxygen in the recovery room. Because of the danger of possible regurgitation and aspiration of gastric contents the patient should not be extubated until he is awake and has intact upper airway reflexes.

Following major trauma, many patients remain unstable in a number of ways. These include blood volume and hemodynamics, temperature, acid-base balance, and coagulation. In some instances pulmonary edema is present as a result of pulmonary trauma, or secondary to previous cardiac ischemia and/or massive fluid load. Intracranial pressure may require monitoring. Intensive care will be necessary, but the process of transfer is not simple. There will be a lapse of time before the patient is settled in the ICU with all monitoring systems functioning, and the ICU staff conversant with the ongoing problems. There are various ways to meet this situation, but guiding principles are as follows.

1) Establish and maintain as much monitored stability as is feasible in the operating room i.e. do not take a "blind leap" to the ICU with a hypovolemic, hypotensive patient whose blood gas and acid-base status is unknown. If necessary, stay in the operating room long enough to correct these defects.

2) Use portable electronic monitoring and mechanical ventilation equipment for the move to the ICU and ensure that these are functioning well before leaving the operating room. In patients with severely impaired cardiorespiratory status, a change to manual ventilation may result in a sufficient change in intrathoracic pressure to cause increased hypotension or intracranial pressure, or to permit a change in lung volume with resulting deterioration in oxygen exchange.

3) Forewarn the ICU, to prepare the necessary ventilation and monitoring equipment, and any other urgently required therapy, such as blood products.

4) On arrival, establish continuity of blood pressure monitoring and of ventilation as first priority. Stay with the patient until all monitoring and support systems are reestablished and the ICU staff is familiarized with the patient's circumstances and orders.

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